THE HEART OF THE MATTER:
CARDIOVASCULAR VULNERABILITY OF BREAST CANCER SURVIVORS
IMPLICATIONS FOR AEROBIC CAPACITY AND CARDIOVASCULAR RISK

Jordan Talmadge Lee

A dissertation defense submitted to the faculty of the University of North Carolina at Chapel Hill in fulfillment of the requirements for the degree of Doctor of Philosophy in the School of Medicine (Interdisciplinary Program in Human Movement Science).

Chapel Hill
2020

Approved By:

Claudio L. Battaglini

Hyman B. Muss

Lee W. Stoner

Erik D. Hanson

Kirsten A. Nyrop

ABSTRACT

Jordan Talmadge Lee: The Heart of the Matter: Cardiovascular Vulnerability of Breast Cancer Survivors. Implications for Aerobic Capacity and Cardiovascular Risk
(Under the direction of Claudio L. Battaglini)

PURPOSE The purpose of this investigation was to improve understanding of the cardiovascular health and aerobic capacity profile of breast cancer survivors (BCS) and the role of community-based exercise to impact these profiles during early cancer survivorship. PARTICIPANTS Thirty-five early stage BCS who were within one year of completing either chemotherapy and/or radiation and twenty-one age-matched, sedentary, non-cancer controls (CTL) were enrolled for this study. METHODS: Applanation tonometry and cuff-based techniques were used to measure arterial stiffness (pulse wave velocity, augmentation index) and central hemodynamics (blood pressure, Buckberg Index). Cardiopulmonary exercise testing (CPET) on a cycle ergometer was used to evaluate aerobic capacity (VO_{2peak}) before and after aerobic and strength exercise training 3 days per week for 16-weeks at a community-based training center. Linear mixed models were used to evaluate arterial stiffness and aerobic capacity between groups before and after exercise training. Exploratory univariate analyses investigated relationships between changes in arterial stiffness and aerobic capacity, respectively, with measures of exercise engagement. RESULTS Arterial stiffness between BCS and CTLs reflected that of healthy normal values at baseline and did not change following exercise. However, exploratory analyses of only BCS revealed significant increase in arterial stiffness regardless primary cancer treatment. Days of aerobic compliance were associated

(R= -0.343, p=0.038) with pre-post change in PWV in a pooled sample. Aerobic capacity (1.2mL/kg/min; 95% CI [0.15, 2.27]; p=0.03) improved equitably between groups following training. Both groups attended 71% of prescribed days. Aerobic compliance was 54% for BCS, 67% for CTL and strength compliance was 29% for BCS and 38% for CTL. CONCLUSION Community-based exercise appears to be a promising route for cancer survivors to improve aerobic capacity, but more studies evaluating vascular health in BCS are needed to better understand our preliminary findings. Efforts to improve exercise compliance in community-based settings may improve ability to target specific physiological outcomes and unique needs of breast cancer survivors.

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CHAPTER ONE: INTRODUCTION

Background

In 2019 alone, over a quarter of a million women will be diagnosed with breast cancer – the most common cancer diagnosis for women in the United States (Cancer Statistics Center, 2018). Decades of work devoted to improving cancer detection, identifying tumors at earlier stages, and advancing treatment technologies have resulted in favorable long-term prognoses for thousands of BCS (Miller et al., 2016). However, the advancements are bittersweet. While breast cancer therapies are powerful tools for fighting tumors, they can also induce a number of life-changing negative side effects including but not limited to peripheral neuropathy, sleep disturbances, loss of strength and endurance, increased fatigue, and decreased functionality that warrant extra care or threaten treatment completion (Kirsten A Nyrop et al., 2018; Schmitz, DiSipio, Gordon, & Hayes, 2015). As the BCS survivor pool continues to grow into the millions, managing the volume of survivors with debilitating side effects becomes a personal and public health challenge (Bluethmann, Mariotto, & Rowland, 2016). In particular, cardiovascular complications and increased risk of cardiovascular events in BCS is of particular concern (Armenian et al., 2017; Patnaik, Byers, DiGuiseppi, Dabelea, & Denberg, 2011). Unfortunately, it has been realized that as BCS age, risk of dying from cardiovascular complications exceeds that of their cancer (Patnaik et al., 2011). The impact is so severe that a specialization termed "cardio-oncology" has developed and first-ever breast cancer/cardiac risk position statements have been made by the American Heart Association (Mehta et al., 2018).

Research has demonstrated that lifestyle risk factors at diagnosis from physical inactivity and/or poor dietary habits in concert with toxic cancer therapies is a particularly dangerous combination for long-term cardiovascular health in the breast cancer population (L. W. Jones, Haykowsky, Swartz, Douglas, & Mackey, 2007). The loss of cardiovascular health/function related to cancer and treatments in BCS is also characterized by exercise intolerance and an attenuated maximal capacity to uptake and utilize oxygen ("aerobic capacity") (L. W. Jones, Courneya, et al., 2012). Aerobic capacity is the gold standard measure for cardiopulmonary fitness, and reflects an individual's integration of cardiac and vascular systems/structures in the body. Loss of aerobic capacity can have a direct impact on patient quality and quantity of life, and impairments warrant specific attention for individual well-being (L. W. Jones, Haykowsky, Pituskin, et al., 2007a; Kaminsky et al., 2013). Lower aerobic capacities have been associated with increased mortality, both cancer and non-cancer specific, increased morbidity, and less favorable patient outcomes (J. B. Peel et al., 2009). Associations between low aerobic capacity and increased mortality following surgery have been observed in specific cancer populations. Unfortunately, aerobic capacities also diminish throughout the cancer continuum, especially during adjuvant therapy, but exercise can provide powerful leverage to improve aerobic capacity in the adjuvant setting (L. W. Jones et al., 2016; Lakoski et al., 2013; Lakoski, Jones, Krone, Stein, & Scott, 2015; J. B. Peel et al., 2009; J M Scott et al., 2018).

As a quantification of whole-body oxygen consumption, aerobic capacities reflect cardiac and vascular integration, and reduced values in BCS suggest impairments related to the organ structures/systems responsible for oxygen uptake, distribution, and utilization (L. W. Jones, Haykowsky, Swartz, et al., 2007; Jessica M Scott, Nilsen, Gupta, & Jones, 2018). Cardiac-specific damage in BCS has been well-studied, but vascular or peripheral (microvascular, muscular)

damage has not received the same attention. However, due to the integration and dependency between cardiac, vascular, and muscular structures of the body, a combination of insults likely contributes to the overall decreased aerobic capacity and increased cardiovascular disease risk observed in BCS. Chemotherapies and targeted therapies, such as anthracyclines and trastuzumab, have known detrimental effects on the cardiac system and developing evidence supports the vascular system may be insulted as well (Jain, Russell, Schwartz, Panjrath, & Aronow, 2017; Mulrooney, Blaes, & Duprez, 2012). It is also possible that a "domino effect" exists: observed cardiac damage in BCS may be downstream from cancer therapy-induced vascular damage, and/or compromised conduit vascular function may impair peripheral microvascular function. The overall effect may be represented by a decreased systemic aerobic capacity and increased susceptibility to future cardiovascular events. However, more work is needed to elucidate the cardiovascular profiles of BCS following treatment and the relationship of these individual systems to overall aerobic capacity. Clarifying the specific cardiovascular components potentially affected by cancer and cancer therapies, how they relate to overall aerobic capacity, and the potential ability to protect or recover their health and function with targeted interventions would provide important advances for the field of cardio-oncology.

Exercise therapy is a well-established method to improve systemic aerobic capacity and certain specific cardiovascular outcomes, and is a standard of care in cardiac-specific rehabilitation for heart failure patients (L. W. Jones et al., 2008). Aerobic exercise has also been shown to improve arterial stiffness (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014). However, the impact of exercise on specific cardiac and vascular outcomes including those related to arterial stiffness and/or peripheral components of the oxygen cascade, has received minimal attention in BCS (Mulrooney et al., 2012). Exercise has been proven a safe and feasible option to significantly

improve cardiorespiratory fitness in BCS but prescriptions have yet to be optimized and survivors still exhibit cardiovascular challenges and fatal future cardiovascular events (Battaglini et al., 2014a; Kearney et al., 2017; Lakoski, Eves, Douglas, & Jones, 2012; McNeely et al., 2006). Additionally, no standardized practice exists to monitor cardiovascular health long-term in BCS, and potential sensitive, diagnostic approaches like cardiac MRI are expensive and logistically challenging (Armenian et al., 2017). More clinically feasible options such as non-invasive oscillometric or tonometric techniques that could be employed consistently would be highly beneficial. In the meantime, clinicians caring for BCS are encouraged to remain acutely aware of potential cardiac complications and quickly evaluate patients who appear symptomatic (Armenian et al., 2017). To maximize effective, patient-centered care, there is an increasing need to identify specific cardiovascular vulnerabilities in breast cancer survivors and to determine feasible and appropriate interventions capable of improving components and overall cardiovascular performance. Exercise may be a powerful solution but more work is needed to evaluate the impact of training on individual cardiovascular components and their overall impact on aerobic capacity (Jessica M Scott et al., 2018). In the scope of long-term cancer care, as the number of cancer survivors continues to grow, the need to accommodate large volumes of people with effective interventions becomes essential, yet challenging, and community-based interventions may be necessary (Bluethmann et al., 2016). Lastly, the ability to identify at baseline which types of patients would benefit from which types of interventions would dramatically improve our ability to streamline patient-centered care and maximize individual outcomes, and should therefore remain a priority in the field.

Statement of Purpose

Cardiovascular disease mortality is a global burden and a particular threat to BCS due to potential cardiac and vascular specific damage from cytotoxic cancer therapies. There is a critical need to evaluate cancer therapy-induced cardiovascular damage in BCS which may be an important contributor to the observed increased cardiovascular risk and decreased aerobic capacity in this population. Furthermore, determining interventions that may improve or protect vulnerable cardiovascular organs/systems will provide patients with means to enhance long-term well-being.

Therefore, the purpose of this study was to compare the cardiovascular and aerobic capacity profiles of BCS who have recently completed primary cancer treatments with otherwise healthy, non-cancer controls (CTL) before and after a 16-week, community-based exercise program. Exploratory analyses investigated the utility of baseline cardiovascular measures as predictors of exercise response (quantified by deltaVO_{2peak}), and also investigated the relationship between baseline $p16^{INK4a}$, a marker of molecular aging, and important measures of clinically and functionally measures of patient outcomes.

This study enhanced our understanding of cardiovascular system outcomes following cancer therapies and in response to community-based exercise training stimuli. These efforts can help lay the foundation for future studies to consider implementing cardio- and vaso-specific protective strategies before or during cancer therapy, and to help maintain and/or improve long-term cardiovascular outcomes of the largest group of cancer survivors in the nation.

Definition of Terms and Abbreviations

Aerobic capacity: The ability of the body to uptake, distribute, and utilize oxygen in the body and is quantified in this study as VO_{2peak} (mL O_2 /kg/min).

Breast Cancer Survivors (BCS): Woman with a confirmed breast cancer diagnosis and includes all phases of the cancer continuum from diagnosis to treatment to decades following treatment completion living with a history of cancer. In this study, BCS were early stage (0-III) survivors who were within one year of completing their primary breast cancer treatments (surgery, chemotherapy, radiation).

Otherwise healthy, non-cancer controls (CTL): Women ≥21 years old without any cancer diagnosis/history or other overt, known health concerns and who exercise two or fewer days per week at enrollment.

VO_{2peak}: peak quantity (mL O_2/kg/min) of oxygen consumed during a cardiopulmonary exercise test (CPET) on a cycle ergometer. VO_{2peak} was calculated as the average of the three highest, five-second averages of recorded oxygen consumption measures during the last minute of a CPET.

Oxygen Cascade: The stepwise flow/movement of oxygen in the body from inhalation/pulmonary diffusion, delivery by the heart, transport by conduit vasculature, and consumption across microvasculature at the peripheral working tissue (in this study, muscles) (Hoppeler & Weibel, 1998).

Cardiovascular profile/components: Measures of cardiac and vascular health outcomes including arterial stiffness (quantified by pulse wave velocity (PWV)), augmentation index (AIx), and Buckberg Index obtained via non-invasive tonometry methods (PWV, AIx, Buckberg).

Community-based exercise program: Refers to the University of North Carolina Get REAL & Heel (GRH) Breast Cancer exercise rehabilitation program for cancer survivors. This is a 3-day per week, supervised group exercise program specifically designed for breast cancer patients and includes both aerobic and strength training customized to each patient's ability.

$p16^{INK4a}$: Tumor suppressor protein that has been evaluated as a biomarker of molecular aging in peripheral T-cells collected from standard venipuncture

Research Aims and Hypotheses

The purpose of this investigation was addressed by two primary aims illustrated in Figure 1. Aim #1 evaluated the cardiovascular profile, primarily arterial stiffness (PWV), of BCS compared to CTL before and after 16-weeks of community-based exercise training. This Aim is addressed in Manuscript One. Aim #2 evaluated cardiorespiratory fitness, specifically aerobic capacity (VO_{2peak}), of BCS compared to CTL before and after 16-weeks of community-based exercise training. This Aim is addressed in Manuscript Two.

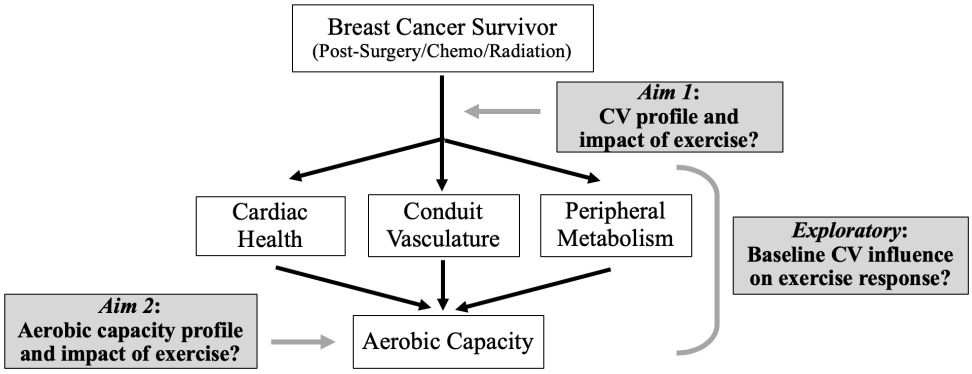


Figure 1. Conceptual model leading to research aims.

Primary and Secondary Aims

***Aim 1:* To determine the cardiovascular profile of breast cancer survivors compared to women without a cancer history before and after a 16-week, community-based exercise program.**

Null Hypothesis 1a: PWV will not differ between BCS and CTL at baseline.

Null Hypothesis 1b: Changes in PWV will not differ between BCS and CTL following participation in community based, exercise training.

***Aim 2:* To determine cardiorespiratory fitness of breast cancer survivors compared to women without a cancer history before and after a 16-week, community-based exercise program.**

Null Hypothesis 2a: VO_{2peak} will not differ between BCS and CTL at baseline.

Null Hypothesis 2b: Changes in VO_{2peak} will differ between BCS and CTL following participation in community based, exercise training.

Exploratory Analyses

In addition to the previously stated Research Aims, three exploratory analyses were also conducted. The first exploratory analysis evaluated the relationship between baseline cardiovascular variables (PWV, AIx, Buckberg Index) with changes in cardiorespiratory fitness (ΔVO_{2peak}) in BCS and CTL. A second exploratory analysis evaluated the relationship between

baseline cardiovascular variables (PWV, AIx, Buckberg Index) with training response (responders ($\Delta VO_{2peak} \geq 2.5$ml/kg/min) vs. non-responders ($\Delta VO_{2peak} < 2.5$ml/kg/min)) in BCS and CTL. A third exploratory analysis evaluated the relationship between baseline $p16^{INK4a}$ biomarker of aging and clinical/functional patient outcomes including but not limited to ΔVO_{2peak}, arterial stiffness, 6MWT, and lean body mass.

Assumptions

1. All of the participants followed the pre-test and post-test guidelines.
2. All of the participants were honest in answering questions related to medical history and physical activity.
3. All participants honestly engaged in exercise at the community-based facility to the best of their abilities.
4. All participants maintained current/normal lifestyles (nutrition, other physical activity) throughout the 16-week study period with the exception of the exercise intervention prescribed by researchers.
5. All participants remained under routine cancer care and long-term therapy (endocrine treatment), as appropriate, and immediately communicate any pertinent health related changes (especially oncologic or cardiovascular related changes) with the research team.

Limitations

1. Baseline evaluation of BCS in this study were completed after primary cancer therapies. Therefore, cardiovascular outcomes pertinent to this study prior to cancer therapy is unknown, subsequently, the changes in outcomes specifically due to cancer therapies cannot be determined but may be speculated with descriptive statistics.

2. Exercise intervention intensity was primarily evaluated using subjective, patient reported exertion (using Borg rating of perceived exertion (RPE) scale) which may be less specific than heart rates or oxygen uptake but is a necessary design for realistic and practical implementation in a community-based, non-randomized controlled design.
3. Negative impacts (both objective and subjective) of long-term cancer related medications (ex: endocrine therapy) may become enhanced over the study duration, however this is standard of cancer care and were accommodated as best as possible during the study.

Delimitations

1. A relatively select sample size of locally-residing women due to need to attend exercise sessions at Get REAL & Heel 3 days per week for 16 weeks.
2. Only women who had completed their major breast cancer anti-cancer treatments within the past year were eligible to participate in the study.
3. Only women who were not currently participating in regular exercise defined as physically active no more than 2 days per week.

Significance

The damaging effects of certain breast cancer therapies on cardiovascular health in combination with existing risk factors places breast cancer patients at particular risk for developing cardiovascular disease (L. W. Jones, Haykowsky, Swartz, et al., 2007). Determining, monitoring, and detecting vulnerable components, affected structures, and clinically relevant deterioration, respectively, is essential for patient quality and quantity of life (Armenian et al., 2017). Implementing and evaluating feasible interventions with cardioprotective potential would enhance our ability to optimally care for cancer patients. As the cancer survivor pool continues to grow, these challenges are both critical and necessary (Bluethmann et al., 2016).

This project aimed to enhance our understanding of the cardiovascular status of BCS who have completed primary cancer therapies compared to women without a cancer history, and the impact of community-based exercise training on their cardiovascular profiles. This study helped maximize the opportunity for patient-centered cancer care by evaluating novel and vital cardiovascular-specific outcomes currently lacking in the literature, and is an important step toward understanding the acute trajectory of cardiovascular health of BCS in the early stages of survivorship.

CHAPTER TWO: LITERATURE REVIEW

Overview

For the purpose of organization, this review of literature is divided into four main sections. The first section provides an overview of breast cancer and associated side effects of treatment. The second section reviews specific cardiovascular toxicities of breast cancer therapies. The third section will discuss cardiorespiratory fitness based on the oxygen cascade and cardiovascular hemodynamics. The fourth section will focuses on the potential benefit of exercise training in the oncology setting for improving cardiovascular physiology, function, and performance.

Section I: Breast Cancer

Breast cancer is the most common malignancy in women; affecting approximately 2.7 million globally each year, and killing approximately one woman per minute per day (Patnaik et al., 2011) The financial footprint of breast cancer is substantial and approximates ~4% of the Gross Domestic Product, roughly 620-740 billion dollars (Bigby & Holmes, 2005). Fortunately, improved early detection, precise medical technologies, better treatment strategies, and robust cancer therapies have resulted in a relatively controlled incidence of breast cancer and a growing pool of survivors (approximately 3.1 million in the U.S. as of 2016) (Bluethmann et al., 2016; Miller et al., 2016; Runowicz et al., 2016; Siegel, Miller, & Jemal, 2015). Surgery, chemotherapy, and radiation cancer therapies have changed over the years to provide more precise, powerful, and effective treatment for breast cancer. However, these same therapies that have successfully

improved disease-free survival (DFS) and overall survival (OS) for breast cancer patients also place healthy cells at risk for damage.

Side Effects of Breast Cancer Treatment

While tumor cells are the primary target for cancer therapies, chemotherapy, for example, is toxic to rapidly dividing cells - a defining feature of cancer (Hanahan & Weinberg, 2000). However, other non-cancerous cells in the body, like those of the gastro-intestinal tract, hair, and skin, are also rapidly dividing. Chemotherapy-induced damage to these otherwise healthy cells can result in undesired and potentially debilitating side effects like nausea, vomiting, neutropenia, thrombocytopenia, fatigue, and paresthesia, among others. If side effects become too severe, cancer therapy can be delayed, require dose reductions, or even be discontinued based on patient recovery response. While a treatment hiatus provides opportunity for patient rebound from negative side effects, a discontinuous regimen may compromise the efficacy of the established benefits of therapy (Hershman et al., 2011). Side effects, both long and short term, can significantly impact a patient's quality and quantity of life (Basch et al., 2017; K.A. Nyrop et al., 2018).

Symptoms from chemotherapy treatment can improve with time following cessation of therapy, however, potentially permanent and severe side effects are possible. The most well-documented, severe, and permanent side effect of breast cancer treatment is congestive heart failure as a result of the most commonly used class of chemotherapy; anthracyclines (Armenian et al., 2017; Floyd et al., 2005). This life-altering condition is obviously highly concerning and recent growing attention to critical cardiovascular issues in cancer survivors has resulted in the emergence of the 'cardio-oncology' subspecialty in medical institutions (Jain et al., 2017). It is becoming increasingly evident that BCS (especially older individuals) can actually be at a higher risk of

dying from CVD than breast cancer, likely due to the 'multiple hit' of poor lifestyle habits, cardiotoxic cancer therapies, and overall autonomic dysfunction (Gernaat et al., 2017; L. W. Jones, Haykowsky, Pituskin, et al., 2007b; Lakoski et al., 2015; Patnaik et al., 2011; J M Scott et al., 2018; Shiovitz & Korde, 2015). Additionally, damage to the cardiovascular system can compromise independence and impair functional capacities potentially altering quality of life (K S Courneya et al., 2003; Paterson, Cunningham, Koval, & St Croix, 1999). Especially as the numbers of BCS grow, efforts to prevent, attenuate, and reverse cardiotoxic consequences of cancer treatments are warranted and necessary (Armenian et al., 2017; Schmitz, Prosnitz, Schwartz, & Carver, 2012).

Section II: Cardiovascular Toxicity of Breast Cancer Therapy

The impact of cancer therapies on the components of the cardiovascular system, the associated effects on the ability to uptake, distribute, and consume oxygen in the body, and the long-term implications of cardiovascular health is a topic of tremendous interest in the medical community. Soundly functioning cardiac and vascular systems are essential for oxygen utilization in the body, and can be quantified as aerobic capacity (measured as VO_2). Breast cancer survivors have demonstrated significant impairments (10-30% decrement) in aerobic capacities across the cancer care continuum which suggests disruption in cardiac and/or vascular systems (Jones, Courneya, et al., 2012). Loss of aerobic capacity is particularly concerning because impairments have been significantly associated with increased mortality, worse symptom burden, increased treatment toxicity, and decreased overall quality of life in cancer patients (K S Courneya et al., 2003; Kerry S Courneya et al., 2014; Herrero et al., 2006; L. W. Jones, Hornsby, et al., 2012). Due to the unique impact therapies may have on the cardiac versus vascular structures, these two systems will be addressed independently below per primary therapy. More is known about cardiac

specific damage than vascular specific damage but natural and physical linkage between the cardiac and vascular system, the nature of cancer therapy administration via intravenous infusion (chemotherapy) and/or central vessel exposure during radiation suggests that the vascular system may be particularly vulnerable to toxic effects of cancer therapies. Evidence suggesting prevalence of vascular injury is increasing and vascular damage from cancer therapy may be a unique contributor to cardiovascular disease risk, may develop independently from cardiac-specific damage, and/or may enhance cardiac specific dysfunction in breast cancer populations (Blaes et al., 2017; L M Jones, Stoner, Brown, Baldi, & McLaren, 2013; Koelwyn et al., 2016; J M Scott, Adams, Koelwyn, & Jones, 2016). Therefore, more attention to understand the impact of primary cancer therapies on both cardiac and vascular structures and their ability to support oxygen utilization in the body is extremely warranted.

Surgery

Surgery is a local, site-specific therapy for breast cancer designed to physically remove the tumor from the body. In early stage breast cancers, surgery usually occurs before chemotherapy but may occur after, depending on the tumor size and adjuvant treatment intention. Tissue samples removed from the tumor during surgery can be used to determine tumor stage, grade and help clarify overall prognosis. The decision for surgery and volume of tumor and breast tissue removed depend on the specific tumor size, location, prognosis, and patient cosmetic desire. A radical mastectomy involves removal of the entire affected breast and is usually performed when the tumor is diffuse or particularly aggressive, or simply by patient desire. Breast conserving therapy (BCT), which includes a lumpectomy plus radiation, is the primary treatment strategy for early stage breast cancer. Lumpectomies remove only the tumor and a margin of normal breast tissue surrounding the tumor while leaving the majority of the breast intact. Breast surgeries are usually

accompanied by lymph node dissection, either sentinel or axillary, that help oncologists determine the likelihood that the tumor has spread to other parts of the body. Sentinel nodes are located close to the breast and are the most likely nodes to contain rogue cancer cells. If evidence of cancer cells exists in the sentinel nodes, a surgeon may complete an axillary lymph node dissection. These additional lymph nodes located peripheral to the breast are removed and help indicate the likelihood of metastasis to the body (Galimberti et al., 2013).

In terms of cardiovascular risks, breast cancer surgery alone has not been associated with long-term cardiovascular disease development.

Chemotherapy

Perhaps the most critical yet challenging goal of cancer treatment is preventing tumor progression and minimizing metastatic potential. Chemotherapy, targeted therapy, and hormonal therapies circulate the whole body to target rogue cancer cells that may have metastatic potential. Chemotherapy, given intravenously or by pill, has proven tremendously successful in preventing recurrence and promoting cancer-specific survival, and is a cornerstone treatment in our arsenal of cancer therapies (Mansour et al., 1989, 1998; Peto et al., 2012). Targeted therapy and hormonal therapy are systemic treatments with use dependent on tumor cell membrane receptor expression characteristics (D. Slamon et al., 2011).

Common classes of chemotherapies include but are not limited to: anthracyclines, antimetabolites, antimicrotubular agents, and tyrosine kinase inhibitors that destroy cancer cells through a variety of mechanisms (Gradishar et al., 2018). The diversity in mechanisms of action (MOA) between different chemotherapies provides beneficial alternatives for cancer treatment in the event patients are not able to tolerate a particular regimen. Anthracyclines are a legacy drug for cancer treatment and are considered an essential medicine by the World Health Organization

(WHO) ("19th WHO Model List of Essential Medicines (April 2015)," 2015). These foundational drugs are the most widely used chemotherapies for systemic treatment of breast cancer, used in over one-third of breast cancer patients (Giordano, Lin, Kuo, Hortobagyi, & Goodwin, 2012; Mulrooney et al., 2012). Mechanistically, anthracycline agents intercalate between base pairs of DNA and RNA, interfere with critical DNA replication enzymes, and induce substantial oxidative damage resulting in tumor cell death (Jain et al., 2017). Common chemotherapy routines including anthracyclines involve four to six cycles of therapy occurring in a two or three-week frequency with drugs given individually or in combination, depending on the regimen selected by the treating oncologist (Gradishar et al., 2018).

Cardiotoxicity of Anthracycline Chemotherapy

Chemotherapy-induced cardiotoxicity from anthracycline therapy is well documented in the literature (Floyd et al., 2005; Jain et al., 2017). First identified in the 1970's, anthracycline-induced cardiotoxicity is dose-dependent with incidence ranging from 3%-48%, based on the cumulative dose received. This discovery led to the development of guidelines limiting a patient's cumulative lifetime dose of anthracyclines to approximately 500mg/m^2 (Von Hoff et al., 1979). However, cardiotoxicity can occur at doses below this threshold and nevertheless, constrains treatment efficacy (Swain, Whaley, & Ewer, 2003; Von Hoff et al., 1979).

Symptomatic anthracycline-induced cardiotoxicity can be acute (within days), early-onset (within the first year of drug administration), or late-onset (greater than one year from drug administration) and is the most severe clinical concern of cancer treatment (Henriksen, 2018). Acute toxicity is the least concerning, usually resulting in transient cardiac rhythm changes, but also somewhat uncommon. Early and late onset cardiomyopathies are initially quantified by declines in left ventricular ejection fraction (LVEF) and can progress irreversibly to congestive

heart failure (CHF), or may become clinically detectable only after permanent damage has occurred (Doyle, Neugut, Jacobson, Grann, & Hershman, 2005; Lakoski et al., 2015; Von Hoff et al., 1979). With a hazard ratio of 3.46 compared to , this specific heart failure imparts an especially poor prognosis for breast cancer patients (Felker et al., 2000). In the absence of standard long-term cardiac-specific follow up practices for cancer patients, effective monitoring of potential cardiotoxicity is logistically challenging (Schmitz et al., 2012). In attempt to capture and treat potential cardiotoxicity as early as possible, a recent review suggested that suspicion for cardiotoxicity in cancer survivors should remain high and standards for evaluation be low (Armenian et al., 2017). Other groups have suggested cardiovascular-specific evaluations be completed in all patients starting adjuvant treatment, regardless the specific therapy (Koelwyn, Khouri, Mackey, Douglas, & Jones, 2012). Needless to say, developing improved strategies to identify patients at high cardiovascular disease risk and implementing cardio-protective approaches to cancer care is highly warranted.

Development of alternative anthracycline analogs with decreased cardiotoxic threat has been attempted but with minimal success (McGowan et al., 2017; Weiss, 1992). However, current research suggests there has been a steady decline in anthracycline use from 2005 until present and taxane-based regimens appear to be slowly replacing anthracyclines (Giordano et al., 2012). Furthermore, recent findings suggest most women at moderate risk of breast cancer recurrence do not necessarily benefit from chemotherapy, and may therefore no longer warrant receipt of the treatment (Sparano et al., 2018). However, use of cardiotoxic therapies has not ended entirely and extended adjuvant treatment regimens are being used in clinical practice; increasing potentially toxic exposure duration. Furthermore, the volume of survivors previously treated with known cardiotoxic agents will still require attention. This is especially important as the demand to care

for the growing number of survivors may outpace the medical providers available to serve (Bluethmann et al., 2016). Efforts to clarify the mechanisms responsible for cardiovascular damage and toxicity will enhance the ability to design and implement cardioprotective strategies.

No single mechanism has been identified as the predominant contributor to anthracycline-induced cardiotoxicity, and the process is indeed complex. It has also been suggested that the mechanisms responsible for tumor cell death are distinct from those that result in cardiac cell death, and/or that cardiomyopathy results when drug-induced damage is combined with particularly harmful lifestyle choices (Menna, Salvatorelli, & Minotti, 2008). Current evidence supports oxidative stress due to mitochondrial dysfunction, ion dysregulation, energy depletion, and disrupted cardiac signaling pathways all contribute to anthracycline-induced cardiomyopathy. As evidenced through some of these speculated pathways, anthracycline toxicity may actually amplify in the body as the drug is metabolized (Mordente, Meucci, Silvestrini, Martorana, & Giardina, 2012).

Oxidative stress is a common and powerful rationale for explaining anthracycline-induced cardiotoxicity but is not absolute. Reduction of anthracycline molecules due to enzymatic and non-enzymatic activity can produce levels of hydrogen peroxide (H_2O_2) above that of normal levels and can result in substantial physical damage to mitochondria (G Minotti, Cairo, & Monti, 1999; Giorgio Minotti, Menna, Salvatorelli, Cairo, & Gianni, 2004). Under healthy conditions, detoxifying enzymes can usually manage clearance of potentially harmful radicals, however, cardiomyoctyes naturally have a decreased capacity to resist oxidative damage compared to other tissues and are particularly compromised with anthracycline therapy (Doroshow, Locker, & Myers, 1980). Mitochondria-based damage from anthracyclines such as membrane disruption, organelle swelling and rupture, and injury to the electron transport chain result in the inability to

properly metabolize fuel substrates for energy which can lead to mitochondrial death. In terms of tumor fighting capacity, this effect has clear benefit. However, the same impact cannot be said for cardiomyocytes. Furthermore, it has been demonstrated that anthracyclines directly damage mitochondrial DNA (mtDNA) of cardiac muscle, but less so skeletal muscle, likely due to intercalation into strands or via production of reactive oxygen species (Adachi et al., 1993; Ashley & Poulton, 2009; Dirk Lebrecht, Kokkori, Ketelsen, Setzer, & Walker, 2005). Unfortunately, mtDNA damage, electron transport chain dysfunction, and reactive oxygen species production can compound and accumulate over time. This latency effect is speculated as the primary reason for development of late-onset cardiomyopathy and irreversible damage (D Lebrecht et al., 2007).

Vascular Toxicity of Chemotherapy

Few studies exist regarding vascular health in BCS, but even low to moderate doses of anthracyclines have resulted in preclinical vascular abnormalities and evidence of poor arterial health, such as increased arterial stiffness, which may predict future cardiovascular events (Chaosuwannakit et al., 2010; Drafts et al., 2013; Grover et al., 2015; Kilicaslan, Piskin, Susam, Dursun, & Ozdogan, 2014; Koelwyn et al., 2016). Postmenopausal BCS who received chemotherapy have demonstrated greater arterial stiffness than pre and peri-menopausal counterparts (Yersal, Eryilmaz, Akdam, Meydan, & Barutca, 2018). Rapid deterioration of vascular health within the first month of anthracycline chemotherapy implies acute damage, but impairments have been documented up to one year following chemotherapy treatment (Drafts et al., 2013; Grover et al., 2015). While markers of aortic stiffness appear to normalize or recover years after therapy, more research is needed to evaluate factors that may enhance this recovery or prevent initial decline. One of only two published studies evaluating cardiac and vascular health in long-term cancer survivors concluded no difference between study groups, yet both participant

groups reported substantial exercise participation; approximately 55 minutes per day (Koelwyn et al., 2016). With exercise as a known promoter of cardiovascular health in healthy and clinical populations, it is possible that participation in exercise was beneficial in improving long-term arterial health following chemotherapy (D J Green, Spence, Halliwill, Cable, & Thijssen, 2011; D J Green, Spence, Rowley, Thijssen, & Naylor, 2012; Daniel J Green & Smith, 2018). However, to our knowledge, no published study exists that evaluates the impact of chronic exercise training on vascular health parameters in BCS. The latter mentioned study that found no difference in arterial stiffness evaluated cancer survivors but included mostly male subjects who were diagnosed at a young age and therefore may have had enhanced ability to withstand damage and/or recover more completely (Kearney et al., 2017). Furthermore, the two previously mentioned studies also found evidence of stress/exercise-induced cardiac-specific dysfunction in survivors despite relatively normal resting measures (Beaudry et al., 2019; Koelwyn et al., 2016). Because the cardiac tissue is perfused/served via central arterial supply, it is possible that preceding/upstream central vascular dysfunction subsequently damaged cardiac tissue, and vascular damage may only be clinically evident when the heart is placed under exertional stress. This elucidates the importance of detecting and monitoring vascular health because it may be the first clinical sign of impending cardiovascular decline (Erbel et al., 2014; Mozos, Borzak, Caraba, & Mihaescu, 2017). Increased surveillance and accelerated detection of vascular dysfunction in concert with effective intervention strategies, potentially exercise, would likely provide critical advances in caring for BCS. Fortunately, robust and non-invasive markers of vascular health, such as arterial stiffness, are feasible to capture and may be successfully implemented in a clinical cancer care setting, but have yet to be extensively studied in the literature (Laurent et al., 2001, 2003; Sutton-Tyrrell et al., 2005; Willum-Hansen et al., 2006).

Targeted Therapy

Unlike the blanket-style approach of systemic chemotherapy, targeted therapies are specific to blocking the growth of a cancer cell via a precise receptor or vulnerable characteristic of that tumor. Trastuzumab (Herceptin®) and pertuzumab (Perjeta®) are two targeted therapies used for treatment of primary and metastatic HER2+ breast cancer tumors, respectively. Both are humanized monoclonal antibodies that act on specific and different sites of the human epidermal growth receptor located on the tumor cell membrane. These drugs prevent dimerization of HER2 receptors, successfully interfering with cell signaling pathways critical to growth and proliferation, which can consequently prevent tumor cell survival (Albini et al., 2011). Trastuzumab has been shown to improve disease free survival by 51% and overall survival by 37% when administered following anthracycline therapy, providing substantial benefit for HER2+ breast cancer patients (Romond et al., 2005; D. J. Slamon et al., 2001; Zeglinski, Ludke, Jassal, & Singal, 2011).

Cardiotoxicity of Trastuzumab Targeted Therapy

While generally less severe than anthracycline-induced damage and potentially less permanent, anti-HER2+ therapies can also induce unwanted cardiac complications like congestive heart failure and/or left ventricular dysfunction (Albini et al., 2011; Tan-Chiu et al., 2005; Zeglinski et al., 2011). Trastuzumab following anthracycline therapy is the most effective combination for HER2+ tumors, improving disease free survival (DFS) by 51% in contrast to non-anthracycline regimens that only confer 39% DFS, yet comes with the risk of increased likelihood of suffering from cardiac damage (Albini et al., 2011; Piccart-Gebhart et al., 2005; Romond et al., 2005; Zeglinski et al., 2011). Concurrent administration of these agents is particularly threatening to the CV system, especially in older patients, increasing incidence of cardiac dysfunction by 27% (Seidman et al., 2002) Therefore, standard of care is to administer these drugs sequentially (Albini

et al., 2011; Zeglinski et al., 2011). While the precision of directed therapies like trastuzumab has contributed substantially to the arsenal of tools available for HER2+ cancer therapy, mechanistically the drug targets a ubiquitous receptor, rendering non-tumor cells susceptible to injury (Sandoo, Kitas, & Carmichael, 2015; Zeglinski et al., 2011). Cardiac tissue expresses human epidermal growth factor receptors, although the degree of expression is debated, resulting in vulnerability to the effects of trastuzumab (Albini et al., 2011). The resulting cardiotoxicity usually presents more quickly than anthracycline-induced damage but manifests similarly as a decline in LVEF. Also dissimilar to anthracycline cardiotoxicity, trastuzumab-induced cardiac decline has been attributed to disruption in Neuregulin1 and ErbB receptor signaling pathways, mitochondrial function, and cellular energetics rather than structural damage of cardiomyocytes (Brero et al., 2010; Lee et al., 1995; Rochais & Fischmeister, 2010; Spallarossa et al., 2010). Permanent damage to the cardiac tissue from trastuzumab is less common than anthracycline-induced damage and recovery of cardiac function is possible following cessation of trastuzumab therapy. Interestingly, some patients are also able to restart anti-HER2 therapy without subsequent cardiac symptoms. However, the therapy is a modern intervention, thus, long term side effects like cardiotoxicity profile are not yet well-known (L. W. Jones, Haykowsky, Swartz, et al., 2007).

Vascular Toxicity of Trastuzumab Targeted Therapy

Extremely limited research is available evaluating the impact of trastuzumab on vascular specific outcomes in breast cancer survivors (Grover et al., 2015). Two published studies evaluating arterial function of BCS found that women treated with trastuzumab targeted therapy demonstrate significantly increased arterial stiffness when compared to age and CV risk factor matched controls, but less so than what has been shown with anthracyclines alone (Grover et al., 2015; Yersal et al., 2018). However, most patients in the previously mentioned studies were also

treated with anthracyclines so delineating the specific impact of trastuzumab alone is complicated. Regardless, pulse wave velocities increased by over 2 m/s in only 4 months following therapy which doubles the clinically meaningful change usually seen in approximately 10 years of aging (C.-Y. Liu et al., 2012; Yersal et al., 2018). More work is needed to determine the specific impact of targeted therapies on vascular health.

Radiation

Radiation treatment for breast cancer occurs in the adjuvant setting following surgery and/or chemotherapy. Radiation uses high energy rays to kill cancer cells which prevents the formation of new cancer cells, halves the risk of death from breast cancer recurrence, and substantially lowers the risk of breast cancer related death ((M. Clarke et al., 2005; Early Breast Cancer Trialists' Collaborative, Darby, et al., 2011; Veronesi et al., 1993). Radiation, in combination with lumpectomy, has been an important and effective advancement for the conservative treatment of breast cancer offering patients minimal surgery yet equivalent survival benefit as mastectomies (Lichter et al., 1992; Shapiro et al., 1998). For more involved breast cancers such as node positive tumors, radiation also has demonstrated benefit for tumor control and overall survival in both pre and postmenopausal (Overgaard et al., 1997, 1999). Usually the whole breast is irradiated, especially if lymph nodes were found to be positive, but localized radiation techniques are being evaluated in clinical trials. Significant improvements in radiation administration techniques have allowed increased precision of treatment and decreased adverse side effects, with decreased CVD mortality of particular interest (Giordano et al., 2005; Patt et al., 2005).

Cardiotoxicity of Radiation

Due to the location of vital organs in proximity to breast tissue that may be targeted, incidental exposure of the heart, lungs, and thoracic vessels to radiation can result in substantial organ and structure damage (M. Clarke et al., 2005; Cuzick et al., 1994; Marks et al., 2005). A staggering 62% increase in cardiac deaths has been observed in women who received radiation therapy for their breast cancer (Yusuf, Sami, & Daher, 2011). Research supports that radiation can damage proper physical contraction of the muscular ventricular wall, leading to perfusion deficits in the heart; especially as more heart volume is included in the radiation field in addition to damage of the cardiac vasculature (Gyenes, Fornander, Carlens, Glas, & Rutqvist, 1996; Marks et al., 2005). Valvular heart disease is recognized especially in women who receive radiation doses in excess of 30 Gray (Hull, Morris, Pepine, & Mendenhall, 2003). However, radiation-induced damage can result independent of detectable changes in left ventricular ejection fraction (LVEF), which is the most widely used cardiac surveillance technique for many cancer patients. The silent development of heart disease in this population further reiterates the need for consecutive cardiac surveillance techniques.

Vascular Toxicity of Radiation

In addition to cardiac wall damage, radiation has been shown to impair the essential elastic properties of the aorta and contribute to increased local arterial stiffening (Kilicaslan et al., 2014; Vallerio et al., 2016). Coronary artery disease and risk of vascular-related death is substantially increased in women treated with radiotherapy ("Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group," 2000).The higher the mean dose of radiation, the greater the rate of major coronary events, with an approximate 7.4% increase in risk per Gray received,

albeit likely related to older techniques not commonly used today (Darby et al., 2013). Improvements in administration techniques, like respiratory gating/breath holding, since the 1970's have resulted in decreased risk of cardiovascular disease in patients treated with radiation (Hooning et al., 2007). While currently speculative without long term prospective data, radiotherapy-induced cardiac perfusion deficits, wall motion abnormalities, and local arterial stiffening may collectively or individually contribute to long term cardiovascular disease development in cancer patients.

Hormonal Therapy

Hormonal therapy is a third example of commonly used systemic therapies for women with HR+ tumors. Tamoxifen (Nolvadex®) is a selective estrogen receptor modulator (SERM) given to block estrogen from reaching estrogen receptors in ER+ and/or PR+ breast cancer cells. Five years of Tamoxifen therapy provides a significant reduction in risk of same-side recurrence, ipsilateral recurrence, and death from breast cancer for ER+ tumors (Early Breast Cancer Trialists' Collaborative, Davies, et al., 2011). Both pre and postmenopausal women can take Tamoxifen while other hormonal therapies called aromatase inhibitors (AIs; letrozole (Femara®), exemestane (Aromasin®), and anastrazole (Arimidex®) are generally used for premenopausal women with ER/PR+ breast cancers (Dowsett et al., 2010). Aromatase inhibitors interfere with the enzyme necessary for producing estrogen in the body, therefore decreasing availability of the hormone ligand and counteracting the growth of HR+ tumor cells. Tamoxifen and AIs are commonly administered in an alternating pattern for approximately 5-10 years in the adjuvant setting (C. Davies et al., 2013; Z. Yu et al., 2017). While AI therapy use and efficacy for breast cancer recurrence is surpassing that of Tamoxifen, decreased serum estrogen, hyperlipidemia, and hypercholesterolemia due to AIs' MOA may be enhancing cardiovascular

specific events and remains a concern (Foglietta et al., 2017; L. W. Jones, Haykowsky, Swartz, et al., 2007). Tamoxifen, on the other hand, appears to elicit cardioprotective effects related to blood lipid profiles due to its actions as an estrogen agonist. Overall, it has not yet been determined whether the cardiovascular disease risk profile differences between the two hormonal therapies are a result of protective effects of Tamoxifen or harmful effects of AI's, but these changes may predispose the survivor to unwanted comorbidities (Foglietta et al., 2017; Thurlimann et al., 2005).

Cardiotoxicity of Aromatase Inhibitors

Estrogen is thought to play a protective role in terms of cardiovascular health based on the relatively low incidence of cardiovascular disease in premenopausal compared to postmenopausal women, and between women and men (Kalin & Zumoff, 1990; Leening et al., 2014). Aromatase inhibitors are primarily prescribed for postmenopausal BCS, many of who present at baseline with existing cardiovascular risk factors and who may further increase risk through behavioral changes like physical inactivity and poor diet during cancer therapy (Irwin et al., 2003; Rock et al., 1999; Wagoner, Choi, et al., 2019; P. W. F. Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). Therefore, additional reduction in circulating estrogen due to effects of aromatase therapy can further exacerbate the potential of developing cardiovascular disease in BCS, especially those who are postmenopausal (Amir, Seruga, Niraula, Carlsson, & Ocana, 2011). Evaluation of large endocrine therapy trials for cardiac safety reveals heterogeneous results related to cardiovascular risk, events and cardiac-specific mortality (Foglietta et al., 2017).

Vascular Toxicity of Aromatase Inhibitors

Aromatase inhibitors are thought to elicit negative effects on the vascular endothelium disrupting vasodilation, coagulation and antioxidant regulation, potentially predisposing survivors to atherosclerosis and/or hypercholesterolemia (Mendelsohn, 2002; Nathan et al., 2001). Women receiving aromatase therapy have demonstrated increased arterial stiffness and less favorable lipid profiles but a distinguished, vascular-specific toxicity due to AI damage versus Tamoxifen protection has not yet been observed (Foglietta et al., 2017; Yersal et al., 2018).

Summary

Primary breast cancer therapies have the potential to significantly disrupt cardiovascular health, with the impact of some treatments more toxic, evident, and/or well-studied than others. Further work is needed to clarify each therapy's damage-inducing mechanism and the organs and tissues that may be most vulnerable. Further, the ability to feasibly and accurately monitor and detect early deterioration in the cardiac and vascular system would likely provide opportunity for earlier intervention and potentially curb the incidence of permanent cardiovascular disease. Additionally, the potential role of complementary therapies such as exercise to protect or promote cardiac and vascular-specific health of BCS in the adjuvant setting warrants investigation.

Section III: Cardiorespiratory Fitness: Oxygen Cascade and Hemodynamics

The Oxygen Cascade

The cardiovascular system is responsible for oxygen transport and utilization in the body. Cancer therapy-induced damage can directly threaten the vigor of the integrated cardiac, vascular and peripheral oxygen-associated structures essential for life. Cardiorespiratory fitness can be

measured directly through maximal exercise testing and is quantified in terms of maximal aerobic capacity or VO_{2max}. This maximal oxygen consumption is also described mathematically in the Fick equation ($VO_{2max} = CO * a\text{-}vO_{2diff}$) as a product of cardiac output (stroke volume * heart rate) times the arterial venous oxygen difference ($a\text{-}vO_{2diff}$). An individual's aerobic capacity is therefore a product of central and peripheral components; the former dominated by the heart and conduit vasculature, and the latter by microvasculature, skeletal muscle, and mitochondria (Hoppeler & Weibel, 1998). In series, these components reflect links in the oxygen cascade – a model describing the flow of oxygen delivery, transport, and consumption. Mathematically, it can be demonstrated that impairments, individual or in combination, in this cascade will result in an overall impaired aerobic capacity (VO_{2max}). Interestingly, decreased aerobic capacity is a well-established phenomenon observed in breast cancer patients and is critical due to the established relationship between depressed maximal aerobic capacities with increased morbidity and mortality (L. W. Jones et al., 2010; Terence Kavanagh et al., 2003). From diagnosis to years beyond, breast cancer patients have demonstrated aerobic capacities up to 30% lower than age-matched, non-cancer controls (L. W. Jones, Courneya, et al., 2012). This loss of aerobic capacity has been observed despite preserved stroke volume, and survivors demonstrate impairments in contractility and an inability to meet functional demand (Koelwyn et al., 2016). Therefore, determinants of oxygen transport other than central cardiac factors must be compromised, but have not yet been well studied in this population.

Peripheral components of the oxygen cascade, like microvascular function, are less well-researched than central components, especially in breast cancer populations, and warrant further evaluation. Furthermore, the vulnerability of the different links in this chain of oxygen utilization, and their associated degree of contribution to overall aerobic capacity are not clearly understood

(Jessica M Scott et al., 2018). Only a handful of studies have concurrently evaluated overall aerobic capacity with potential determinants in BCS, and have observed central performance impairments with implication of peripheral deficiencies, especially at higher workloads (Beaudry et al., 2019; L. W. Jones, Haykowsky, Pituskin, et al., 2007b; Koelwyn et al., 2016). Improving understanding of vulnerable cardiovascular components in potential need of surveillance, will allow researchers the opportunity to propose and design interventions specific to protecting or repairing vulnerable links as a way to preserve systemic oxygen consumption.

From a prevention and treatment perspective, it is important to recognize many newly diagnosed breast cancer patients present at baseline with exercise intolerance and substantial cardiovascular disease risk factors such as physical inactivity and obesity due to lifestyle characteristics and habits (Beaudry et al., 2019; Calle, Rodriguez, Walker-Thurmond, & Thun, 2003; C. A. Clarke, Purdie, & Glaser, 2006; L. W. Jones, Haykowsky, Swartz, et al., 2007). While these initial risk factors approximate that of the general population, further decreases in physical activity from diagnosis to survivorship in BCS can enhance weight gain, even with stable caloric intake, exacerbating an already unhealthy cardiovascular profile and impaired aerobic capacity (Beaudry et al., 2019; Irwin et al., 2003; Rock et al., 1999). Increasing evidence supports that long-term sedentary lifestyles in women with breast cancer accelerates cardiovascular aging resulting in compromised performance as a whole, even before cancer therapy administration (Beaudry et al., 2019). Compounded with cardiotoxic cancer therapies, this milieu of insults (termed “multiple hit”) has the potential to severely disturb both short and long term cardiovascular outcomes in BCS, especially if no interventions are implemented to encourage lifestyle changes (L. W. Jones, Haykowsky, Swartz, et al., 2007; Jessica M Scott et al., 2018).

Cardiovascular Hemodynamics: Central Aspects

The first two components of the Fick equation (stroke volume and heart rate) depend on central cardiac and arterial health. Arteries in the body are structured to allow stretching and contracting based on blood volume shifts with large arteries acting as both a conduit and cushioning system, best represented by the actions of the aorta during heart contractions. Vascular compliance of large arteries is desirable for healthy vascular function but naturally decreases down the arterial tree as peripheral arteries are more muscular and less elastic than their proximal counterparts (Nichols & McDonald, 1972). As the heart pumps and ejects blood into the vasculature (stroke volume), pressure waves propagate through the circulatory system. This coupling of cardiac and vascular compliance is directly related to exercise capacity (Hundley et al., 2001; Kass, 2005). Pressure waves are amplified or dampened through a series of highly complex interactions based on the distensibility, architecture of vessel walls, and changes or bifurcations of the vessel channels as they extend into the periphery (Laurent et al., 2006). As arterial stiffness increases in vessels via aging, disease, or structure, forward-traveling pressure waves exuded by the heart can be propagated or reflected off harder vessel walls with increasing speed (Boutouyrie et al., 1992). This speed of travel can be quantified by carotid-femoral PWV, the gold standard measure of arterial stiffness, and an independent predictor of cardiovascular events and mortality (Laurent et al., 2001, 2003). The stiffer an artery, the faster a wave propagates through the circulation and is reflected back on organs like the heart, potentially damaging the organ and/or compromising pumping action (Coutinho, Turner, & Kullo, 2011; Laurent et al., 2006). Amplification of the central pulse pressure (at the heart) due to increased velocity of reflected pressure waves and poorer microvascular health can be described as the augmentation index (AIx). PWV and AIx are related but differ in that PWV describes regional arterial stiffness

(i.e. in the area of assessment: radial, brachial, carotid-femoral), and AIx changes based on systemic arterial stiffness influenced by heart rate, whole-body reflected wave amplitudes, and PWV (Kim & Braam, 2013). Nonetheless, greater arterial stiffness (i.e. indicated by faster PWV and higher AIx) indicates less elastic, more collagenous vasculature and a less favorable cardiovascular profile (Sutton-Tyrrell et al., 2005; Weber et al., 2004). Clinical conditions such as diabetes and peripheral artery disease can result in compromised vascular health as exhibited by increased PWV (Benetos, Laurent, Hoeks, Boutouyrie, & Safar, 1993; Boutouyrie et al., 1992; O'Rourke, Staessen, Vlachopoulos, Duprez, & Plante, 2002). While significantly less studied compared to diabetes and peripheral artery disease, cancer survivors also exhibit increased arterial stiffness as measured by PWV, likely due to varying vascular-related toxicities from cancer therapies (Mozos et al., 2017; Souza et al., 2018). This unfavorable vascular profile may be a contributor to the increased incidence of cardiovascular mortality observed in BCS.

From a cardiac-specific perspective, depending on timing, pressure waves reflected back on the heart can amplify central pressure placing a higher workload demand on the cardiac system. Similar to consequences of long-term afterload pressure seen in other clinical pathologies, this effect can damage vessels and associated tissues, and can compromise the volume of blood ejected (stroke volume) into the body (Laurent et al., 2006). Pressure waves that collide with the heart during systole (faster PWV) augments afterload pressure at the left ventricle, increasing pulse pressure (increased AIx), decreasing stroke volume, and inducing higher mechanical stress on the heart. Conversely, collision during diastole (slower PWV) is beneficial and enhances perfusion of the cardiac tissue via coronary arteries (decreased AIx). Balancing the heart's physical pumping demand with the requisite to supply its own tissue with oxygen is critical to cardiac performance, as the heart itself only perfuses during diastole (Hoffman & Buckberg, 2014). If stroke volume is

compromised (for example due to anthracycline-induced cardiotoxicity), the heart must increase contraction rate (heart rate) to maintain cardiac output. This is a natural response of the cardiac system observed under stress or during exercise but may become less transient if the heart/vasculature becomes chronically pathologic. Over time, if stroke volume cannot be maintained and heart rate increases to conciliate, perfusion of the heart may be compromised which increases risk of cardiac ischemia (Hoffman & Buckberg, 2014). An index using diastolic pressure, systolic pressure, and time integrals over a cardiac cycle has been developed using characteristics derived from a validated central pressure waveform (Hwang et al., 2014). This value is termed the Buckberg Index and reflects cardiac subendocardial viability; a parameter of diastolic function. While index values are not specifically intended to diagnose ischemia, serial measures may capture changes that illustrate functional deterioration and help identify those at risk of diminishing cardiac performance (Budinskaya et al., 2017; Hoffman & Buckberg, 2014). This measure, derived from the waveform of validated and automated tonometry systems used for pulse wave analysis, has been minimally studied and never reported in the breast cancer literature, to the best of our knowledge (Butlin et al., 2013). The Buckberg index, in addition to PWV and AIx, could be an important, non-invasive, hemodynamic measure to obtain serially when monitoring patients like BCS who have particular cardiovascular concerns.

Non-Invasive Measurement of Central Cardiovascular Health

Pulse wave velocity, AIx, and Buckberg Index can be quickly and reliably captured with clinically feasible, automated, non-invasive technologies such as the FDA-approved, AtCor SphygmaCor XCEL devivce (Hwang et al., 2014; Williams et al., 2006). This device quantifies pressure waves at the periphery, and based on a validated transfer function, describes the central pressure characteristics at the heart (producing AIx and Buckberg Index values) (Butlin et al.,

2013). Central aortic pressures and characteristics are superior to peripheral pressures in describing cardiac stress, however, these technologies are not generally utilized in standard oncology clinics (Wassertheurer et al., 2010). Failing to evaluate central pressures, AIx, and Buckberg indices may compromise more detailed understanding of patient cardiovascular health status. In terms of BCS who are at higher risk of cardiovascular and coronary artery disease due to potentially cardiotoxic therapies, serial cardiovascular surveillance with the previously described non-invasive technologies may offer unique supplemental diagnostic and prognostic value for identifying important, centrally-located cardiovascular vulnerabilities (Harris et al., 2006; L M Jones et al., 2013). However, it should be recognized that values such as the Buckberg Index obtained from pulse wave analysis are derivatives, not direct measurements, and should therefore be interpreted with caution until further direct validations exist.

Cardiovascular Hemodynamics: Peripheral Aspects

The latter portion of the Fick equation (a-vO_{2diff}) is predominately driven by skeletal muscle, especially during exercise, and reflects microvascular and mitochondrial function as peripheral components related to oxygen utilization (Hoppeler & Weibel, 1998). These components of the oxygen cascade have not received extensive evaluation in BCS, but limited evidence suggests function is compromised (Didier et al., 2017; Ederer et al., 2016). While mechanisms of action between cardiotoxic damage and tumor cell damage from chemotherapy may differ, mitochondria have emerged as mutual primary cellular targets of anthracycline therapy. These organelles are responsible for extracting oxygen from microvasculature, managing oxidative stress, balancing calcium concentrations, and producing sufficient energy through aerobic metabolism. Certain chemotherapies used in treatment of breast cancer elicit their tumor-killing effects by disrupting or destroying proper mitochondrial function (Henriksen, 2018;

Mordente et al., 2012). However, the somewhat ambiguous nature of chemotherapy negatively impacts functional tissue like skeletal muscle which is essential for producing movements required for activities of daily living and exercise(Ashley & Poulton, 2009; Poole, Copp, Ferguson, & Musch, 2013). Marked loss of volume of functional, force-producing tissue, and/or impairments in ability to extract or utilize oxygen in the mitochondria limits functional capacity and is a significant concern for BCS (A A Kirkham, Bland, Sayyari, Campbell, & Davis, 2016; Kutynec, McCargar, Barr, & Hislop, 1999; Mordente et al., 2012). These consequences of chemotherapy could be mathematically quantified and vindicated as contributors to decreased systemic aerobic capacity by minimizing the a-vO_{2diff} variable in the Fick equation. While limited data exists, research using infrared spectroscopy suggests impairments in cancer survivors' abilities to properly deliver and extract oxygen during exercise and is speculated to be a result of mitochondrial dysfunction (Didier et al., 2017; Ederer et al., 2016). Fortunately, non-invasive techniques using near infrared light spectroscopy (NIRS) have provided researchers and clinicians means to evaluate surrogate markers of mitochondrial function by monitoring deoxyhemoglobin (HHb) signals in microvasculature of muscles during exercise. Based on light absorption and refraction properties, different wavelengths of light are absorbed by deoxy and oxyhemoglobin allowing researchers to distinguish the two proteins in vessels approximately 1-2mm in diameter (Mancini et al., 1994). As a muscle completes more aerobic work, the consumption of oxygen and production of deoxyhemoglobin should increase, reflective of properly functioning microvasculature and skeletal muscle mitochondria. The rate of consumption over time, especially when evaluated in series in the same individual, may help identify potential impairments in microvascular circulation and mitochondrial function. NIRS only provides a local "snapshot" of microvascular status, and has some limitation and assumptions for proper use, but is a highly

feasible and validated measure when used appropriately (Lucero et al., 2018; Mancini et al., 1994). NIRS has been extensively used in clinical populations such as peripheral artery disease and diabetes mellitus, but has been minimally implemented in cancer patients, and never in a group of all breast cancer survivors to the best of our knowledge (Barroco, Sperandio, Reis, Almeida, & Neder, 2017; Lanfranconi et al., 2014; Layec et al., 2016).

Section IV: Exercise for Cardiorespiratory Health and Fitness

Well designed and implemented exercise can have an important role for improving cardiorespiratory health, fitness, fatigue, and quality of life among other factors in the breast cancer population (Battaglini et al., 2014b; A A Kirkham et al., 2016; McNeely et al., 2006; Schmitz et al., 2010). Recent publications support exercise as an effective adjuvant therapy for increasing cardiorespiratory fitness in BCS and other clinically relevant outcomes (A A Kirkham et al., 2016; J M Scott et al., 2018). Interestingly, while exercise can positively impact multiple organ systems, enhance overall cardiovascular reserve capacity, and is an established therapy to improve exertional intolerance for patients with heart failure (Pandey et al., 2015), the same utility has been less consistently appreciated in the breast cancer population (L. W. Jones, Haykowsky, Swartz, et al., 2007; Lakoski et al., 2012; Mora, Cook, Buring, Ridker, & Lee, 2007). However, it has been shown that increasing levels of exercise is associated with a decrease in incidence of cardiovascular events in women with non-metastatic breast cancer (L. W. Jones et al., 2016). All-cause and cancer-specific mortality have been reduced by 13% and 15%, respectively, in non-cancer populations following an increase in cardiorespiratory fitness of approximately 3.5mL/kg/min (1 MET) (Barlow et al., 2012; Kodama et al., 2009; Myers et al., 2002).

A significant gap in the field of exercise oncology is the lack of clarity between structured exercise interventions and specific biologic/physiologic cardiovascular changes they elicit,

especially as they relate to overall cardiorespiratory fitness. Cardiovascular outcomes other than cardiorespiratory fitness are rarely reported but warrant attention as they may be important and unique indicators of heart, macro, and microvascular health and may be more feasibly obtained and monitored in clinic settings than a CPET (Jessica M Scott et al., 2018). Determinants of aerobic capacity (i.e. those representative of the components in the Fick equation) have also been minimally studied in concurrence with systemic aerobic capacity measurements (Beaudry et al., 2019; L. W. Jones, Haykowsky, Pituskin, et al., 2007a) Systemic cardiorespiratory fitness can be improved with properly designed and implemented exercise, which suggests cardiac and vascular determinants supporting the overall oxygen consumption are improving either independently or as a system. This phenomena is well-described in non-cancer populations (M. G. Wilson, Ellison, & Cable, 2016) and supporting and speculated mechanisms will be explained below. However, the impact of exercise training on individual components, especially those related to vascular health and peripheral oxygen metabolism, have not been well studied or reported in BCS (Beaudry et al., 2019; J M Scott et al., 2018). Evaluating these more intricate relationships may provide an enhanced understanding of specific vulnerable components of a BCS's cardiovascular system following cancer therapy, and the unique contribution of components to systemic oxygen consumption. Long term, these components may develop as new targets for consecutive surveillance or intervention throughout a BCS's journey.

Mechanisms of Exercise-induced Changes

Exercise has long been appreciated as a strategy to broadly improve cardiovascular health. Mechanisms of exercise-induced improvements revolve around structural and functional changes in the myocardium and endothelium (M. G. Wilson et al., 2016). The degree of benefits/changes are generally dependent on the type, intensity, duration, and frequency of exercise activity but in

general, greater amounts of exercise appear to maximize cardiovascular health (T Kavanagh, 1983; M. G. Wilson et al., 2016). Athletes commonly exhibit superior fitness, enlarged heart structures, and lower resting blood pressures when compared to sedentary controls as a result of continuous engagement in structured physical activity(M. G. Wilson et al., 2016). These changes promote cardiovascular efficiency and enhance exercise capacity due to improvements in ability to uptake, distribute, and utilize oxygen within the body. Therefore, exercise training can be used, alone or in concert with pharmacologic interventions, to target vulnerable systems and improve outcomes for at-risk populations.

Cardiac Benefits of Exercise Training

The majority of cardiac hypertrophy in the heart following exercise training relates to the effect of hemodynamic loads during exertion inducing enlargement of cardiomyocytes. Endurance exercise training (running, cycling, swimming etc. for long periods of time) elicits blood volume stress on the heart due to an increase in venous return and end diastolic volume of the left ventricle. This stimulus causes immediate improvements in ejection fraction/stroke volume due to the Frank-Starling stretch-contract reflex (Shiels & White, 2008). Chronic endurance training causes the heart to elongate by adding sarcomeres in series, and to increase long-axis torsion or "wringing" which improves overall cardiac output and concurrent contractility (Mihl, Dassen, & Kuipers, 2008; Nakatani, 2011). Improvements in cardiac output directly enhance systemic aerobic capacity as described previously in the Fick Equation. Resistance or strength training elicit pressure stress, specifically increased afterload, on the heart due to occlusion of downstream vessels by contracting muscles. In order to counteract afterload pressure and ensure ejection of blood from the heart, contraction force at the heart must increase. Cardiac tissue responds to chronic afterload pressure stimuli by adding sarcomeres in parallel, eventually thickening the walls of the ventricles and

increasing force-producing potential (Mihl et al., 2008). However, increases in cardiac contractile strength due to strength training has shown minimal impact on overall aerobic capacity in BCS, unlike the adaptations of endurance training, but provide other beneficial systemic effects pertinent to BCS (A A Kirkham et al., 2016; Sasso et al., 2015; Schmitz et al., 2010).

Vascular Benefits of Exercise Training

In healthy populations, repeated or chronic exercise can induce substantial improvements in vascular function and structure that in turn contribute to reduced cardiovascular risk (Daniel J Green & Smith, 2018). The same effects have not been thoroughly studied in cancer populations, although similar adaptations may occur, but may provide particular benefit for this vulnerable population through similar mechanisms. During acute exercise, K+, H+, and CO_2 released from active muscle in combination with the effects of sheer stress inside vessel walls, result in release of nitric oxide (NO) in blood vessels. Shear stress is essential for vascular adaptation and triggers the release of nitric oxide from healthy endothelium. In healthy systems, NO acts as a potent vasodilator which enhances muscle blood flow and perfusion, allowing for enhanced oxygen delivery (Daniel J Green, Maiorana, O'Driscoll, & Taylor, 2004). Repeated bouts of exercise, and therefore repeated exposure to hemodynamic loads and shear stress, result in structural and functional changes in vessels that enhance vasodilatory effects, improve wall:lumen ratios, increase capillary networks, and reduce systemic arterial resistance, benefitting the vascular system as a whole (D J Green et al., 2011; Daniel J Green & Smith, 2018). These changes result in an enhanced ability to accommodate blood volume and pressure stress, may reduce unwanted central pressures at the heart, and may augment both the delivery of oxygen and removal of waste in working muscle (D J Green et al., 2012; Daniel J Green et al., 2004; Sugawara et al., 2007). These responses are evident in populations with intact autonomic systems but in

populations like BCS with demonstrated autonomic dysfunction and potential endothelial damage, the effects may be dampened or absent (Lakoski et al., 2015; J M Scott et al., 2014). Two recently published studies observed attenuated blood flow response in cancer survivors, which negatively impacts proper utilization of oxygen at working tissue, but mechanisms responsible for these decrements are not yet understood (Didier et al., 2017; Ederer et al., 2016). Furthermore, it is relatively unknown the impact or potential benefit of chronic exercise training on blood flow in cancer populations.

Oxidative Stress Benefits of Exercise Training

Exercise naturally produces free-radicals in mitochondria of working cells but chronic exercise training reduces oxidative damage, improves antioxidant enzymes, and reduces inflammation by upregulating redox-sensitive defense mechanisms (Hoppeler & Weibel, 1998; Mordente et al., 2012). Chronic training, especially endurance, upregulates mitochondrial biogenesis as a response to the demand for increased oxygen consumption, improved fatty acid oxidation, and increased ATP production. Increased mitochondrial density and number in a working muscle provide the means for improved volume and efficiency of oxygen extraction from the blood and can (in addition to vascular effects) directly increase the latter portion of the Fick equation, increasing overall aerobic capacity. Exercise-induced oxidative stress has also been speculated as a potential cardioprotectant via the neuregulin protein signaling pathway (Peng, Chen, Lim, & Sawyer, 2005). This is the same pathway disrupted in HER2+ breast tumors and exercise-effects may be particularly intriguing in this subset of survivors. Unlike muscle-specific benefits, vascular-specific benefits from chronic oxidative stress stimuli from exercise training are not yet well understood but studies are advancing (Daniel J Green, Hopman, Padilla, Laughlin, & Thijssen, 2017).

Response Heterogeneity and Power of Predictors

While most research presents primary study outcomes like ΔVO_{2peak} in terms of mean response, the heterogeneity of response both within and between study outcomes in BCS has recently become more appreciated (J M Scott et al., 2018). Some patients may respond more/less than others to particular exercise interventions or medical therapies. This has become a particular interest in the field of exercise oncology, especially related to patient-centered care, and has highlighted the potential utility of baseline predictors. The ability to stratify patients by risk profiles into appropriate intervention modalities at baseline using feasibly obtained physiological biomarkers would vastly improve the ability to provide the most effective, appropriate and targeted treatments to the right patients. While gold standard evaluations like a cardiopulmonary exercise testing (CPET) or cardiac MRI's can be used at baseline to risk stratify patients, costs, logistics, and feasibility complicate implementation. In terms of cardiovascular risk predictors in BCS, there is no consistent approach or clinical indicator/biomarker used to evaluate long-term outcomes (Armenian et al., 2017). Indication of cardiovascular damage may not become evident until approximately 5-10 years after treatment completion which necessitates the need for long-term surveillance in this population (Bulten et al., 2014). The non-invasive cardiovascular measures proposed in this study may help provide clinicians and researchers with feasible, potentially prognostic tools to evaluate and monitor patient outcomes consecutively long term and thereby improve our ability to detect changes (L M Jones et al., 2013). Blood biomarkers are also receiving attention as potential powerful indicators of long-term outcomes. The protein encoded by the tumor suppressor gene $p16^{INK4a}$ has recently been evaluated and established as a biomarker of aging (Y. Liu et al., 2009; Tsygankov, Liu, Sanoff, Sharpless, & Elston, 2009). Cancer patients treated with chemotherapy have demonstrated accelerated molecular aging in peripheral blood T-

cells (Sanoff et al., 2014). Interestingly, the 10-14 years of molecular aging observed via increased p16 ^{INK4a} expression in the previously mentioned study approximates the same aging phenomenon related to aerobic capacity observed in cancer patients following therapy (L. W. Jones, Courneya, et al., 2012). The relationship between p16 ^{INK4a} and VO_2, and other functional or clinical outcomes, has yet to be evaluated but warrants further investigation (Sanoff et al., 2014).

In summary, the primary gaps in the literature and field of exercise oncology that this study intends to reduce include a paucity of data regarding vascular health profiles of BCS and evaluating how exercise participation may change arterial health of BCS. Further goals include determining how components of the oxygen cascade, such a vascular health outcomes, influence or associate with changes in aerobic capacity following exercise training.

CHAPTER THREE: METHODOLOGY

Subjects

Two cohorts of women were recruited for the proposed study. One group was early stage, non-metastatic BCS who were within one year of completing primary cancer therapy (surgery, chemotherapy, radiation), and were otherwise free from overt cardiovascular, metabolic, orthopaedic complications. The second group was an age and physical activity matched group of women who did not have a cancer history and were otherwise healthy. Both groups required physician clearance to participate and were cleared by a cardiologist before completion of any maximal exercise testing. Both groups completed study-related testing (described later) on 2 days at baseline, and then completed 16-weeks of progressive, supervised aerobic and strength training exercise at the UNC GRH exercise facility, followed by 2 days of post testing mirroring pre-testing.

Recruitment

Clinical Research Associates (CRAs) identified potential study participants through a review of daily clinic schedules for patients seen at the North Carolina Cancer Hospital. The CRAs secured the approval of the treating oncologist prior to approaching the patient about the study. Get REAL & Heel was open to patients seen at other sites, provided they met eligibility criteria described previously and had proof of clearance for participation from their oncologists via email or letter. Non-cancer controls were be recruited by research team members using flyers, emails, and word-of-mouth contact in the local community. All interested persons were screened and consented on a consecutive first come first served bases. Potential participants were contacted by

research team members to discuss the study and allow survivors time to ask any questions. Those interested in participating in the GRH study were asked to sign a UNC IRB-approved informed consent form before completing any study related assessments.

Instrumentation

A Physical Activity Readiness Questionnaire (PAR-Q) and a medical history questionnaire were used to determine whether or not approval by physician would be required to take part in the study prior to officially signing consent to participate. The short version of the International Physical Activity Questionnaire (IPAQ) was used to confirm current physical activity participation in both groups. Literature supports breast cancer survivors report substantial levels of physical inactivity throughout the cancer care continuum, so exercise participation was not used as an exclusion in our breast cancer survivors (Kwan et al., 2012). To best mirror this population, recruited control participants did not complete more than two days of structured exercise at baseline.

A portable stadiometer (Perspective Enterprises, Portage, MI) was used to measure height (to the nearest 0.5 cm) and weight (to the nearest 0.1 kg). A Hologic (Discovery W) Dual X-ray Absorptiometry (DEXA) was used to assess body composition. An electrocardiography system (GE Medical Systems, Milwaukee, Wisconsin) was used to obtain 12-lead ECG tracings for cardiologist review. The SphygmaCor XCEL device (AtCor Medical, Sydney, Australia) was used to collect PWV, AIx, Buckberg Index, and other descriptive hemodynamic measures at rest. A Polar telemetry system (Polar Electro Inc., Lake Success, NY) was used to monitor heart rate during maximal exercise testing. A Lode electronically-braked cycle ergometer was used to complete an incremental 15 watt/min cardiopulmonary exercise test with complete gas exchange

analysis using ParvoMedics metabolic system. The UNC GRH exercise program facility was used for the 16-week exercise training intervention.

Research Design Overview

In this non-randomized study, all subjects completed two laboratory visits prior to (pre-test) and immediately following (post-test) a 16-week supervised exercise intervention as illustrated in Table 1. Both laboratory visits were conducted in the Exercise Oncology Research Laboratory (EORL) in the department of Exercise and Sport Science at UNC-Chapel Hill. Pre and post testing were completed within a two-week window. The first day of testing included: fasted body composition, 12-lead ECG evaluation, fasted and resting cardiovascular measures, and familiarization to the exercise test on the cycle ergometer. The second day of testing included the true maximal exercise test on the cycle ergometer with a 3-minute post completion lactate measurement. The 16-week exercise intervention included a combination of progressive aerobic and strength training for 3 small group sessions per week at approximately 1 hour per session at the UNC GRH exercise facility. Post-testing followed the exact same format as pre-testing (minus ECG) and occured over a two-week timeframe immediately following conclusion of the 16-weeks of exercise training.

Table 1. Study assessment and intervention overview.

Pre-Test Day 1	Pre-Test Day 2	Intervention	Post-Test Day 1	Post-Test Day 2
• DEXA • Ultrasound • Cardiovascular measures • ECG • Blood draw • 6MWT • CPET familiarization	Maximal CPET	16 weeks progressive, supervised aerobic and strength training at UNC Get REAL & Heel	• DEXA • Ultrasound • Cardiovascular measures • Blood draw • 6MWT • CPET familiarization	Maximal CPET

General Procedures

After subjects demonstrated interest to participate in this study and met baseline inclusion criteria (clear medical history, ≤2 days/week exercise, physician approval if needed), subjects were informed of pre-assessment guidelines to follow in the day(s) prior to physical fitness pre and post-testing and were scheduled for pretesting in the EORL. This included being fasted for most of the day one assessments and no caffeine for either testing day, but participants were encouraged to stay hydrated with water. On the first day of pre-testing, subjects read and signed an informed consent form and were assigned a 4-digit identification code. The primary investigator verbally insured the subject adhered to pre-assessment guidelines. The primary investigator collected demographic information of each subject including age, race, sex, height and weight. Cancer-specific information was collected from electronic medical records for survivors who agreed to participate and release related information.

Following demographic data collection, each subject completed in the following order: one DEXA assessment, one ultrasound scan of the *vastus lateralis,* resting cardiovascular measurements (AIx, Buckberg Index, PWV) taken in duplicate and averaged for analysis, one resting 12-lead ECG, one blood draw for complete blood count and $p16^{INK4a}$, one 6-minute walk test (6MWT), two timed up-and-go tests with the fastest time recorded for analysis, and a familiarization session on the bike including wearing a mask and completing submaximal exercise up to 75% of heart rate reserve. Participants were required to be fasted (overnight) for the first five assessments on day one but were encouraged to bring and consume a light snack before the walking test and bike familiarization.

Following the first day, research team members obtained cardiologist review and approval of the 12-lead ECG tracing, and scheduled the participant for the second day of testing.

The second day included a maximal exercise test on the cycle ergometer. Participants were fitted with appropriately sized metabolic mask for gas exchange analysis. Participants completed warm up then an incremental (15 watt/min) ramp maximal exercise test on the cycle ergometer. Following completion of testing days, participants were enrolled in the 16-week exercise intervention. Following completion of the intervention, participants were scheduled to return to the EORL for post-testing and completed the same assessments in the same order as pre-testing. The blood draw was not completed at post testing.

Assessments

Height and Body Mass

Subject's height was measured without shoes, standing with their back against the stadiometer and looking straight ahead. Body mass was measured without shoes and in minimal clothing using an electronic scale.

Body Composition

Total body weight-mass (BW) and compositional aspects of lean body mass (LBM), fat tissue mass (FM), and percentage body fat (% BF) was examined for patient demographics using standard DEXA screening procedures.

Non-invasive cardiovascular measurements

Gold standard measures of arterial stiffness including PWV and AIx, in addition to other hemodynamic variables, were collected using the using the SphygmorCor XCEL device (AtCor Medical, Sydney, Australia) following standard manufacturer guidelines and protocols (following 10-15 minutes of supine rest). For *pulse wave analysis,* an inflatable cuff was placed around the upper arm. Survivors had the cuff placed on the non-surgical side to avoid any complications with lymphedema and control subjects were standardized to the left side.

Contralateral placement of the cuff has been shown to yield congruent readings (Hwang et al., 2014). The cuff as electronically inflated/deflated and central and peripheral blood pressures, AIx, and Buckberg Index were measured by the device and software. Measures were taken in duplicate and averaged for analysis. For *Pulse Wave Velocity*, participants lied in a supine position with a blood pressure cuff on upper thigh of one side of the body to detect femoral pulse, and a handheld tonometer at the ipsilateral carotid artery. Segmental measurements between the cuff and the tonometer were made and were necessary for the software to estimate the linear distance the pressure wave travels in the conduit vessel of interest. The tonometer was placed on the carotid artery and the leg cuff inflated electronically. Once a sufficient pulse wave was detected, the carotid-femoral PWV reading was captured over 10 seconds. Measures were repeated twice or until there was no more than a 10% difference between measures. PWV was automatically calculated as the distance between the detected carotid artery pulse and the detected femoral artery pulse divided by pulse transit time.

Blood Draw

As part of an exploratory analysis (described in statistical analysis section) evaluating a novel biomarker of aging, $p16^{INK4a}$, a complete blood count (CBC) and $p16^{INK4a}$ was assessed via intravenous blood sample for all participants. Blood draws took place after the resting body composition and vascular measures on the first day pre-testing. $p16^{INK4a}$ was assessed using standard blood draw techniques from a 10mL blood sample in an EDTA tube. A CBC with differential was completed and was necessary to normalize biomarker expression to the total lymphocyte count. De-identified samples were delivered to the Sharpless laboratory in the Lineberger Cancer Center for $p16^{INK4a}$ analysis. Blood samples were labeled with anti-CD3 microbeads for T cell population prior to purification using AutoMACS pro (Miltenyi biotec). T

cells with purity exceeding 90% were used for RNA extraction. TaqMan RT-PCR were performed in duplicates and 18S were used as controls to measure the expression of $p16^{INK4a}$. Additionally, TaqMan includes control samples of known $p16^{INK4a}$ and were run as additional methodological control.

6-Minute Walk Test

The 6-minute walk test is a clinically feasible test used to assess aerobic endurance and will be completed following resting cardiovascular measures on the first day of testing. Participants were encouraged to walk as quickly as possible around a 50-yd rectangular course for a total of 6 minutes. Participants had to complete the testing at a walk; jogging or running was not be permitted. Participants were verbally encouraged for maximal possible effort throughout the testing. A member of the research team tallied the number of laps completed to the nearest 5yd. Final distances were converted to meters upon completion.

Cardiopulmonary Exercise Test (CPET)

Participants were required to familiarize with the electronically braked cycle ergometer and mask used for the CPET at the end of day one. Participants completed an identical protocol to the maximal test, including the strength progression and use of the Borg RPE scale, but were stopped at ~75% of their heart rate reserve (HRR) on day one. The maximal CPET was completed on day two and is described in detail below.

On day two, study participants were fitted with the oxygen sensor on the right thigh and rested for 5-10 minutes before being fitted with the mask on the bike. Participants began sitting quietly on the cycle ergometer for 3-minutes while the researchers collected resting metabolic data. The first stage of the test began as a 2-minute unloaded warm up at 0 watts followed by a 3-minute loaded warm up phase of 20 watts. Following the warm up stages, the wattage/workload increased

continuously by 15watts/min until test termination. Termination of the test was determined by subject reaching volitional exhaustion and signaling to stop the test, VO_2 plateau or decrease with increase in exercise intensity, or an abnormal subject response to the test was observed and therefore the research team terminated the test (however, did not occur). This protocol has been previously successfully implemented in other clinical populations (Wilkerson et al., 2011). Heart rate and RPE were continually monitored and recorded throughout the testing. Blood lactate was collected by fingertip puncture 3-minutes after the completion of the maximal CPET.

Get REAL & Heel Exercise Intervention

Following testing, participants completed exercise training 3 days/week for 16 weeks at the UNC GRH Exercise Facility. Exercise was a combination of both strength and strength exercise and was designed to progressively increase to a moderate-high workload but adapted to each participant as necessary. *Aerobic exercise* included a variety of options including walking, cycling, elliptical, etc. For the first 2 weeks of exercise training, exercise volume and intensities began at 10-15 minutes at low intensity of 50-60% of the participant's heart rate reserve (HRR) with a corresponding RPE between 8-11. For participants who were deconditioned, exercise duration may have been reduced by 5-10 minutes. The goal was for participants to achieve 30 minutes of moderate intensity aerobic exercise by mid to end of the 16-week program using 65-75% HRR with a respective RPE between 12-14 (Table 2).

Table 2. Progression of aerobic training exercise prescription.

AEROBIC EXERCISE		**WEEK 1-2**	**WEEK 3-7**	**WEEK 8-16**
• Treadmill • Stationary bike • Elliptical • Stepper	Duration (min)	10-15	10-30	30
	Intensity	Low		Moderate
	RPE	8-11		12-14

Strength exercises targeted large muscle groups in the upper body, lower body, and core to improve strength, balance, and functionality. Each session of strength training lasted approximately 30 minutes. Two sets of each exercise were performed for 10-15 repetitions with intensity progressing in weeks 1-5 from light to moderate (RPE 7-13). After week 5, attempts were made to increase the intensity from moderate to high (RPE 14-15) for 2 sets of 10 repetitions of each exercise. Exercises targeting major muscles groups included: lateral raises wall push-ups, rows, squats, bridge, plank, reverse sit up, shrugs, tandem stance, and lateral pulldown. Modifications to these exercises were made for any existing injuries, orthopedic limitations, or sequela from anti-cancer treatments (Table 3).

Table 3. Progression of strength training exercise prescription.

STRENGTH EXERCISE		**WEEK 1-2**	**WEEK 3-5**	**WEEK 5-16**
• Body weight • Resistance bands • Machine • Dumbbells	Duration (min)	30		
	Intensity	Light to moderate		High
	RPE	7-13		14-15
	Sets x Reps / exercise	1x15	2x10-15	2x10

Training progression was accomplished slowly, starting with 1 set of strength exercises using no weight or very light weight in the first two weeks of training with the number of repetitions achieving 15, then increased based on the participant's ability and limitations up to 2 sets during weeks 3-5 of training. As participants progressed to tolerate increased resistance, a balance component was carefully added to the training regimen. This included performing strength exercises with a level of complexity that challenged postural control.

All exercise training sessions was recorded in a participant log stored in a locked filing cabinet at GRH. This log contained information about the time, mode, amount and intensity of exercise completed per session and the corresponding RPE's. With safety as the utmost priority,

all participants were continuously monitored and supervised during all phases of the exercise sessions at GRH.

Participant adherence and compliance were quantified using exercise logs to determine the exercise dose completed over 16-weeks. Adherence reflects attendance (ATT), simply the number of days participants came to the GRH facility out of the total days possible in 16 weeks (48 days total). Aerobic compliance (aCOMP) was calculated as the number of days (out of 48) where participants completed ≥80% of the prescribed duration at the prescribed intensity. Strength compliance (sCOMP) was calculated as the number of days (out of 48) where participants completed ≥80% of the prescribed volume (sets x reps) at the prescribed intensity.

Sample Size Estimate

Sample size estimates were calculated a priori and were based on the primary outcome of aerobic capacity. Arterial stiffness analysis was evaluated for power post hoc. Published systematic reviews and meta analyses support exercise therapy to increase aerobic capacity in breast cancer survivors by approximately 2.3 - 2.8 mL/kg/min (Battaglini et al., 2014b; J M Scott et al., 2018). We opted for a change of 2.5mL/kg/min. The sample size required was 26 total participants using magnitude-based inferences, but oversampling was performed to account for potential dropouts and missing data.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY) and jamovi open source computer software (The jamovi project, version 1.2.5) . Baseline descriptive statistics (means (SD); percentages for categorical variables) were computed to summarize participant demographics and breast cancer diagnosis/treatment characteristics at baseline and to summarize participant attendance and

compliance with the exercise intervention. Independent t-tests were used to compare groups at baseline, and to compare exercise attendance and compliance following training. Cohen's *d* was calculated for exercise attendance and compliance measures, using the difference between the outcome means for the BCS and CTL groups divided by the pooled SD. For interpretation of effect sizes, Cohen's "rules of thumb" were used: small=0.20, medium=0.50, and large=0.80 (Cohen, 1977).

Because the purpose of this study was also to evaluate the impact of community-based exercise training on arterial stiffness and aerobic capacity, univariate linear regression models were used to evaluate associations of pre-post change in PWV (deltaPWV, adjusted for MAP) and pre-post change in VO_{2peak} (delta $VO_{2peak,}$ adjusted for age) with days since end of treatment (EOT), days of exercise attendance (ATT), days of aerobic exercise compliance (aCOMP), and days of strength exercise compliance (sCOMP) in the BCS group. For exploratory purposes, univariate analyses were then repeated using the pooled sample (BCS plus CTL). Due to sample size limitations, multivariable analyses were not conducted.

***Aim 1:* To determine the cardiovascular profile of breast cancer survivors compared to women without a cancer history before and after a 16-week, community-based exercise program.**

Null Hypothesis 1a: PWV will not differ between BCS and CTL at baseline.

Null Hypothesis 1b: Changes in PWV of BCS and CTL will not differ between following participation in community based, exercise training.

For Hypothesis 1a, a linear mixed model was used to assess the effects of time (pre vs. post) and group (BCS vs. CTL) on PWV. Models used fixed effects of time and group and a random effect of subject with adjustment for mean arterial pressure (MAP). The α-level was set a

priori for all statistical procedures at < 0.05. If time-by-group interactions were not significant, the final models estimated the main effects of group and time.

Aim 2: ***To determine the aerobic capacity of breast cancer survivors compared to women without a cancer history before and after a 16-week, community-based exercise program.***

Null Hypothesis 2a: VO_{2peak} will not differ in BCS than CTL at baseline.

Null Hypothesis 2b: Changes in VO_{2peak} of BCS and CTL will not differ following participation in community based, exercise training.

For Hypothesis 2a, a linear mixed model was used to evaluate the effects of time (pre vs. post) and group (BCS vs. CTL) on VO_{2peak}. Models used fixed effects of time and group and a random effect of subject with adjustment for age. The α-level was set a priori for all statistical procedures at < 0.05. If time-by-group interactions were not significant, the final models estimated the main effects of group and time.

Exploratory Aim 1: ***To determine the relationship between baseline cardiovascular variables (PWV, AIx, Buckberg Index) with changes in aerobic capacity (ΔVO_{2peak}) in breast cancer survivors and women without a cancer history.***

Exploratory Aim 2: ***To determine the relationship between baseline cardiovascular variables (PWV, AIx, Buckberg Index) with training response (responders ($\Delta VO_{2peak} \geq 2.5$ml/kg/min) vs. non-responders ($\Delta VO_{2peak} < 2.5$ml/kg/min)) in breast cancer survivors and women without a cancer history.***

<u>Exploratory Aim 3</u>: To determine the relationship between baseline p16^{INK4a} and clinical/functional patient outcomes including but not limited to ΔVO_{2peak}, arterial stiffness, 6MWT, and lean body mass.

Due to the exploratory nature of Exploratory Aim 1, 2, and 3, no specific hypotheses were tested. Exploratory aims were assessed using univariate linear regression analyses to determine the association of baseline characteristics with the dependent variable (ΔVO_{2peak}).

CHAPTER FOUR: MANUSCRIPT ONE

Background

With ever-increasing survival rates among women with early breast cancer (DeSantis et al., 2019), the risk of dying from cardiovascular disease (CVD) exceeds that of dying from breast cancer (Armenian et al., 2017; Patnaik et al., 2011; Sturgeon et al., 2019). Cardiac-specific damage is well recognized and congestive heart failure is the most concerning cardiovascular risk for BCS, especially those treated with anthracycline chemotherapy (Henriksen, 2018; Jain et al., 2017). Heart failure can be assessed using echocardiograms to detect changes in resting left ventricular ejection fraction (LVEF) (Felker et al., 2000) and while not a standardized practice, is typically monitored during treatment or when survivors become symptomatic, which can be years beyond diagnosis (Armenian et al., 2017; Jain et al., 2017; Schmitz et al., 2012). Therefore, cardiac monitoring and evaluation may be logistically challenging to coordinate. There is also concern that ventricular dysfunction may not be detected at rest (standard testing procedure) but, instead, only when the cardiovascular system is taxed with exercise (Beaudry et al., 2019, 2018; Foulkes et al., 2019; Koelwyn et al., 2016, 2016). Deterioration in cardiac performance may therefore be unintentionally missed until overt enough to induce noticeable changes at rest, which is likely indicative of permanent damage.

Alternative to cardiac-specific damage and less studied to date, substantial vascular-specific damage has been detected in BCS with even low to moderate doses of cardiotoxic cancer therapies and within the first year of survivorship, long before heart failure may develop

(Chaosuwannakit et al., 2010; Didier et al., 2017; Drafts et al., 2013; Ederer et al., 2016; Grover et al., 2015; Jain et al., 2017; Mulrooney et al., 2012). Precisely how the heart is damaged by cancer therapies is a topic of on-going research but vascular-specific changes may occur upstream of cardiac-specific damage (Khouri et al., 2012; A. F. Yu & Jones, 2016; Zagar, Cardinale, & Marks, 2016). Cardiac tissue is perfused by the aorta and coronary arteries; therefore, one hypothesis is that cancer treatments may cause acute stiffening of central vascular structures. This, in turn, may increase afterload on the heart and damage cardiac tissue, which may lead to ventricular dysfunction, heart failure, and/or overall CV fitness decline (L. W. Jones, Courneya, et al., 2012; Laurent et al., 2006). Therefore, vascular health decline may be an early clinical sign of impending CV damage or increased CV risk, but there is a paucity of data related to vascular health profiles of BCS and more work is needed (Armenian et al., 2017; Erbel et al., 2014; Mehta et al., 2018; Mozos et al., 2017).

Fortunately, valid and non-invasive techniques, such as pulse wave velocity (PWV) and pulse wave analysis (PWA), are available to ascertain vascular health status (Gotzmann et al., 2019; Laurent et al., 2006; Milan et al., 2019; Nakagomi, Shoji, Okada, Ohno, & Kobayashi, 2018). Carotid femoral PWV (cfPWV) is the gold standard to evaluate central arterial stiffness and is captured via arterial tonometry (applied pressure sensor) (Laurent et al., 2001, 2003) and PWA provides measures of other hemodynamic variables related to central and peripheral blood pressure, pulse pressure wave reflections, and an index of myocardial oxygen (J. I. Davies & Struthers, 2003; Kim & Braam, 2013) .Two 2010 meta-analyses demonstrated the prognostic value of arterial stiffness and central pressures as independent predictors of future CV events and all-cause mortality in some clinical populations and in the general population, but have yet to be extensively studied in clinical oncology (L M Jones et al., 2013; Lynnette M Jones, Stoner,

Brown, Baldi, & McLaren, 2019; Vlachopoulos, Aznaouridis, O'Rourke, et al., 2010; Vlachopoulos, Aznaouridis, & Stefanadis, 2010a).

Of the limited existing data in oncology patients, treatment with anthracycline chemotherapy and radiation have been associated with increased arterial stiffness (Mozos et al., 2017). Fortunately, two studies suggest aortic stiffness may normalize or recover years after cancer chemotherapy, but further research is needed to evaluate factors that may contribute to this recovery process or prevent initial decline in cancer survivors. (Grover et al., 2015; Koelwyn et al., 2016). Exercise is a known promoter of CV health in the general population, has shown promise to improve arterial stiffness in patients with coronary artery disease, and may be beneficial to BCS vascular health following chemotherapy (D J Green et al., 2011, 2012; Daniel J Green & Smith, 2018; Oliveira, Ribeiro, Alves, Campos, & Oliveira, 2014). In one study evaluating cardiac and vascular health in long-term BCS, no difference was found between survivor and control groups; however, both groups self-reported substantial exercise engagement (about 55 minutes/day) (Koelwyn et al., 2016). To our knowledge, only one study has evaluated the impact of exercise training on arterial stiffness in BCS and found significant improvement in aortic PWV following 12 weeks of circuit training (Lynnette M Jones, Stoner, Baldi, & McLaren, 2020). However, in the two previously mentioned studies, survivors were approximately 7 years post treatment completion (Lynnette M Jones et al., 2020; Koelwyn et al., 2016). The impact of exercise training on vascular health acutely following treatment completion (within ~1-2 years) has yet to be explored.

Research evaluating the vascular health profile and the potential benefit of interventions such as exercise on vascular outcomes in women with breast cancer would further our understanding of vulnerable components of the cardiovascular cascade in this population

(Lynnette M Jones et al., 2019; J M Scott et al., 2016). Advances in this area of research may also generate improved CV monitoring and management strategies clinicians can use in the future to optimize patient-centered care. The current study aimed to profile the cardiovascular system of women with early breast cancer who have recently completed primary cancer treatment, and to evaluate the impact of a 16-week community-based exercise training program on arterial stiffness compared to an age-matched control group of women who are cancer-free.

Methods

Study Overview

In this non-randomized study, two groups of women (one BCS, one non-cancer controls) of similar age and activity level were recruited (Figure 1). Women completed two days of exercise testing (pre) in a research laboratory and then asked to complete 16-weeks of exercise training at a local community-based program before repeating exercise testing (post). The study was approved by the Protocol Review Committee of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center and the Institutional Review Board at UNC Chapel Hill. All participants provided written informed consent.

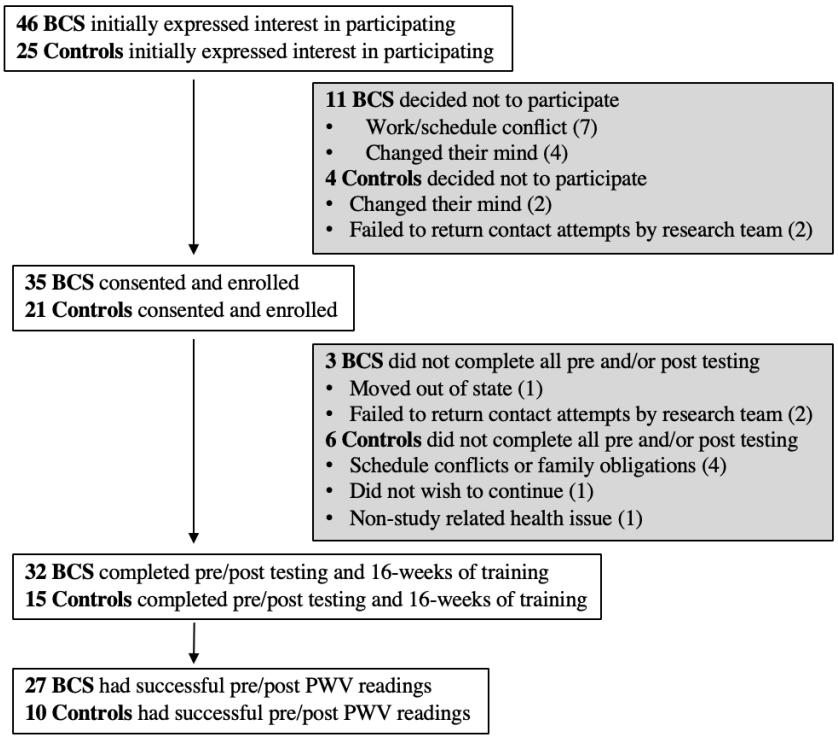


Figure 1 Recruitment and retention

Study Participants

Breast cancer survivors had been diagnosed with early-stage (0-III) breast cancer and were within one year of completing primary therapy (chemotherapy, radiation, surgery). Participants in the CTL group were age-matched, did not have a history of cancer, and self-reported they were physically active no more than 2 days per week. Both groups were free from overt cardiovascular, metabolic, or orthopedic limitations as reported by medical history questionnaire, and were cleared by cardiologists and oncologists (BCS only) prior to participating in the study. Participants in the BCS group were recruited from the Medical Oncology clinic at the North Carolina Cancer Hospital, and by word of mouth from local oncologists and cancer centers. Participants in the CTL group were residents from local cities

including Raleigh, Durham, Chapel Hill and surrounding areas recruited via electronic and paper fliers and word of mouth.

Intervention

For both groups, the 16-week intervention entailed supervised, progressive, aerobic and strength exercise training three days a week for approximately one hour per day (Table 1).

Table 1 Exercise training progression at the Get REAL & Heel Exercise Program

AEROBIC EXERCISE		**WEEK 1-2**	**WEEK 3-7**	**WEEK 8-16**
• Treadmill • Stationary bike • Elliptical • Stepper	Duration (min)	10-15	10-30	30
	Intensity	Low		Moderate
	RPE	8-11		12-14
STRENGTH EXERCISE		**WEEK 1-2**	**WEEK 3-5**	**WEEK 5-16**
• Body weight • Resistance bands • Machine • Dumbbells	Duration (min)	30		
	Intensity	Light to moderate		High
	RPE	7-13		14-15
	Sets x Reps / exercise	1x15	2x10-15	2x10

The supervised training took place at the UNC Get REAL & Heel (GRH) Exercise Program for cancer survivors, an off-campus facility at a convenient location in the community. Participants were asked to maintain their current lifestyle habits outside of GRH training in order to best evaluate the program-specific effects. A variety of equipment for both aerobic and resistance/strength training has been used at GRH to adapt to individual participant fitness and mobility needs which allows trainers the ability to maximize patient safety and exercise engagement. For example, participants could choose treadmills, stationary bikes or ellipticals for aerobic work and dumbbells, resistance bands, or machine weights for strength training, depending on survivor ability and comfort. The specific prescription design is presented in Table 1. Participants were encouraged to challenge themselves to safely engage at their prescribed

workloads, with increasing exercise intensity and duration/volume over time. The priority for training staff was to bring participants safely "up to speed" to attain weekly exercise goals reflective of current national guidelines (Campbell et al., 2019).

Training records were maintained by exercise staff to track participant attendance and compliance over 16 weeks. Attendance (ATT) was calculated as the number of days participants came to the facility out of 48 total days of training opportunity. Aerobic compliance (aCOMP) was calculated as the number of days the participant achieved ≥80% of prescribed duration at the prescribed intensity using Borg Rating of Perceived Exertion (RPE) (Borg, 1973). Strength compliance (sCOMP) was calculated as the number of days the participants achieved ≥80% of prescribed strength volume (sets x repetitions) at the prescribed intensity using Borg RPE (Borg, 1973).

Overview of Procedures

All study participants completed laboratory visits prior to (pre-test) and immediately following (post-test) the 16-week exercise intervention. Both laboratory visits were conducted in the Exercise Oncology Research Laboratory (EORL) of the UNC Department of Exercise and Sport Science. These measures were collected after approximately 15 minutes of supine, fasted rest using the SphygmorCor XCEL device (AtCor Medical, Sydney, Australia) via brachial pressure cuff-based technique on limbs on the non-surgical side of BCS and on left side for CTLs following standard manufacturer guidelines and protocols. Measures and methods for collecting are described below and summarized in Table 2 (Hwang et al., 2014).

Table 2 Study Measures and Equipment

Variable (Equipment used)	**Explanation**
Whole Body Densitometry (Dual X-Ray Absorptiometer, DXA)	Body composition • Normal Body Fat for females ≥50y ~16-25% (Jeukendrup & Gleeson, 2018) • Higher values generally indicative of poorer health similar to BMI but unlike BMI, distinguishes body composition (fat mass, fat free mass)
Carotid-Femoral Pulse Wave Velocity (m/s) (Sphygmacor XCEL)	• Gold standard technique for arterial stiffness, independent predictor of cardiovascular risk and mortality (Laurent et al., 2001, 2006; Vlachopoulos, Aznaouridis, & Stefanadis, 2010a) • Lower values desired as indicative of better vascular compliance • Mean PWV ~8 m/s at <50 ys old (Mitchell et al., 2010; (Reference Values for Arterial Stiffness, 2010)), increases linearly with aging: ~6-8%/decade • 1m/s change considered clinically relevant (Guerin et al., 2001; Vlachopoulos, Aznaouridis, & Stefanadis, 2010a) • BCS treated with anthracycline therapy show increases in PWV by ~4m/s within first few months of survivorship (Chaosuwannakit et al., 2010; Drafts et al., 2013)
Complimentary Vascular Hemodynamics (Sphygmacor XCEL) 1. Central (cSBP) and peripheral blood pressure (SBP, DBP) 2. Mean Arterial Pressure (MAP) 3. Augmentation Index (AIx) 4. Buckberg (BUCK) Index and Double Product	1. Central pressure (norms ~undefined) speculated as better predictors of CV risk than peripheral (norm ~120mmHg, increases with age) (McEniery, Cockcroft, Roman, Franklin, & Wilkinson, 2014) 2. Indicator of perfusion pressure, norm: 70-100mmHg, minimum of 60mmHg required, excess of 100mmHg indicative of poorer vascular health (DeMers D, 2019) 3. An index of pulse wave reflection, AIx describes the amplification of central systolic pressure due to systemic arterial stiffness. Therefore, lower values are desired. Derived from the brachial waveform using validated transfer function.(Butlin et al., 2013; Laurent et al., 2006; McEniery et al., 2005) 4. Indices of myocardial oxygen supply and demand o Buckberg: Associated with functional performance and QOL. Pressure and time ratio reflect resting measure of myocardial oxygen supply and demand. Has been suggested heart failure patients are best managed when index is >150% (Mannion et al., 2017) o Double product: product of systolic blood pressure and pulse rate, index of myocardial oxygen consumption, predicted CV mortality in coronary artery disease patients. (Gobel, Norstrom, Nelson, Jorgensen, & Wang, 1978) o Higher Buckberg index and lower double product desired

Carotid-femoral PWV: After supine for 15 minutes, a BP cuff was placed on the thigh in line with the femoral artery for calculation of PWV. Using a custom-built level caliper, path length was measured from the carotid artery on the same side as the thigh cuff to the top of the cuff. The caliper avoids body contours that may muddle path length and strictly measured the length of the descending aorta. A tonometer was placed on the carotid artery on the neck on the same side as the cuff, and PWV was collected when wave form and quality control were recognized by the SphygmoCor. All PWV measures (SphygmoCor XCEL; AtCor Medical, Itasca, Illinois) were collected in the supine position in duplicate (triplicate if >10% difference) and the closest two values averaged.

Pulse wave analysis (PWA) was obtained by using oscillometric pressure waveforms (SphygmoCor XCEL AtCor Medical) recorded on the arm opposite the involved breast for BCS and right side for CTL using a brachial cuff following standard manufacturer guidelines. An aortic pressure waveform was generated from averaged heartbeat waveforms from SphygmoCor XCEL. Peripheral BP (systolic: SBP, diastolic: DBP) was measured and central BP (cSBP) was estimated using a generalized pressure transfer function of the brachial pressure waveform derived at the arm (Butlin et al., 2013). Augmentation index (AIx) is the augmentation pressure defined as the maximum systolic pressure minus the pressure at the inflection point. AIx is expressed as a percentage of central pulse pressure and is a validated estimation of augmented cardiac pressure analogous to afterload due to the summation of outgoing and returning arterial wave reflections during systole (Laurent et al., 2006). Buckberg index and double product are indicators of myocardial oxygen supply and demand derived from blood pressure and time integrals (Hoffman & Buckberg, 2014). Buckberg is calculated as the diastolic to systolic pressure-time integral ratio and double product is central systolic blood pressure times pulse rate.

Patient demographics and cancer-specific clinical data were extracted from the electronic medical record (EMR) by a member of the research team.

Power Calculations

This study was part of a larger study powered on a different primary outcome. At the time of data collection, the effects of exercise training on PWV of BCS had not been investigated, though previous reports demonstrated 6.6m/s (~95%) increase in arterial stiffness in BCS following completion of chemotherapy (Chaosuwannakit et al., 2010) and changes of 1 m/s, have been considered clinically meaningful in other populations (Vlachopoulos, Aznaouridis, & Stefanadis, 2010b). Post hoc power analysis of our data using an alpha level of 0.05, 80% power and sample sizes of 27 and 10 revealed we were powered to detect an effect size of 1.06.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY) and jamovi open source computer software (The jamovi project, version 1.2.5) . Baseline descriptive statistics (means (SD); percentages for categorical variables) were computed to summarize participant demographics and breast cancer diagnosis/treatment characteristics at baseline (Table 3) and to summarize participant attendance and compliance with the exercise intervention (Table 6). Independent samples t-tests were used to compare groups at baseline, and to compare exercise attendance and compliance following training. Cohen's *d* was calculated for exercise attendance and compliance measures, using the difference between the outcome means for the BCS and CTL groups divided by the pooled SD. For interpretation of effect sizes, Cohen's "rules of thumb" were used: small=0.20, medium=0.50, and large=0.80 (Cohen, 1977).

Three linear mixed models were assessed in this study. The first evaluated the effects of time (pre vs. post) and group (BCS vs. CTL) on PWV, SBP, DBP, MAP, HR, AIx, cSBP, BUCK, and central double product (Table 5). The second evaluated the effects of time (pre vs. post) and cancer treatment group (BCS with chemo vs. BCS without chemo; BCS with radiation vs. BCS without radiation (Table 6). The third assessed the effects of time (pre vs. post) and group by menopausal status (premenopausal BCS vs. postmenopausal BCS) on PWV (Table 6). All models used fixed effects of time and group and a random effect of subject with adjustment for MAP (PWV only). The third model also accounted for age. The a-level was set a priori for all statistical procedures at < 0.05. If all time-by-group interactions were not significant, final models estimated the main effects of group and time on all outcomes.

Because the purpose of this study was to evaluate the impact of community-based exercise training on arterial stiffness, univariate linear regression models were used to evaluate associations of pre-post change in PWV (deltaPWV) with days since end of treatment (EOT), days of exercise attendance (ATT), days of aerobic exercise compliance (aCOMP), and days of strength exercise compliance (sCOMP) in the BCS group (Table 8). For exploratory purposes, univariate analyses were then repeated using the pooled sample (BCS plus CTL) (Table 9). Due to sample size limitations, multivariable analyses were not conducted.

Results

Thirty-five women with breast cancer were enrolled, of which 32 completed all pre and post testing and 27 had successful pre and post PWV readings. Twenty-one non-cancer control women were enrolled, of which 15 completed all pre and post testing and 10 had successful pre and post PWV readings. Reliable PWV reading could not be detected in a few of the participants (BCS n=5; CTL n=5) due to anatomical thickness around the neck preventing a clear pulse wave

signal, which decreased our sample size. Those excluded were otherwise very similar to women with complete data. The final sample of 27 BCS and 10 CTL with complete data was analyzed for the current study (Figure 1). There were no differences at baseline between the two groups for demographic or clinical outcome variables (Table 3). Based on power analysis calculations, the interpretation of our findings should be approached as strictly preliminary.

Table 3 Baseline Characteristics of Breast Cancer and Control Groups

	Total Sample n=37	**Breast Cancer** n=27	**Control** n=10	***p*-value**
Demographics				
Age (yr)	54 (11)	53 (12)	56 (9)	0.434
Height (cm)	166 (7)	167 (7)	163 (7)	0.146
Weight (kg)	73 (10)	74 (10)	71 (10)	0.481
BMI Categories (kg/m^2)				
Normal (18.5 to <25)	35%	37%	30%	1.0
Overweight (25 to <30)	49%	44%	60%	0.476
Obese I (30 to <35)	11%	11%	10%	1.0
Obese II (≥35)	5%	8%	0%	1.0
Body Fat (%)	40 (5)	40 (6)	40 (6)	0.625
Lean mass (kg)	41 (5)	41 (5)	40 (5)	0.657
Postmenopausal (%)	62	59	70	0.710
Race (Caucasian, %)	92	88	100	0.548
Clinical Variables				
Pulse Wave Velocity (m/s)	7.7 (1.1)	7.7 (1.1)	7.7 (1.2)	0.936
Resting heart rate (bpm)	66 (10)	67 (10)	63 (11)	0.365
Central Systolic Blood Pressure (mmHg)	116 (11)	115 (11)	118 (9)	0.584
Systolic Blood Pressure (mmHg)	126 (11)	125 (11)	128 (9)	0.596
Diastolic Blood Pressure (mmHg)	79 (7)	79 (7)	79 (5)	0.980
Mean Arterial Pressure (mmHg)	94 (8)	93 (9)	94 (5)	0.855
Augmentation Index (%)	27 (10)	27 (11)	28 (7)	0.658
Buckberg Index (SEVR)	145 (21)	145 (22)	144 (20)	0.873
Double Product (mmHg*bpm)	7607 (1319)	7687 (1377)	7392 (1188)	0.553
Breast Cancer Details				
Tumor Stage				
0		4%		
I		31%		
II		46%		
III		19%		

Hormone Receptor Status			
Positive		81%	
HER-2 Status			
Positive (all received Trastuzumab)		26%	
Surgery			
Lumpectomy		74%	
Mastectomy		26%	
Time Since End of Treatment			
<3 months		61%	
3 to <6 months		19%	
6 to <9 months		8%	
9 months to 1 year		12%	
Treatment Received			
Radiation		78%	
Chemotherapy		59%	
Both		44%	
Cardiotoxic Therapies			
Anthracycline		19%	
Trastuzumab		26%	
Anthra + Tras		4%	
Endocrine Therapy			
Aromatase Inhibitor		41%	
Tamoxifen		33%	

Both BCS and CTL groups had the same mean number of training sessions (34 days of 48 planned, p=0.938) for an average attendance rate of 71% (Table 4). Differences in aerobic compliance between groups did not reach statistical significance but demonstrated a medium to large effect size (Cohen's $d = 0.60$), with CTL's having a greater number of compliant days than BCS (32(10) vs 26(9) days). CTL participants also completed a greater number of days of strength training compared to BCS (18(3) vs 14(5), Cohen's $d = -0.83$, p=0.031); albeit compliance with strength protocol was less than 40% in both groups.

Table 4 Attendance and Compliance (out of 48 total days of training opportunity)

	Breast Cancer mean (SD) n=27	**Control** mean (SD) n=10	**Cohen's *d* Effect Size**	***p*-value**
Intervention Attendance (days)	34 (9)	34 (10)	0.00	0.938
Aerobic Compliance (days)	26 (10)	32 (9)	-0.60	0.112
Strength Compliance (days)	14 (5)	18 (3)	-0.83	**0.031**

For BCS and CTL, there were no significant time x group interactions for PWV (Figure 2) or any other hemodynamic variables included in analysis, nor any significant main effects of time or group (Table 5).

Table 5 Results from linear mixed model of cardiovascular outcomes after 16-weeks of community-based exercise training in breast cancer survivors and non-cancer controls

		Mean (SD)				
Outcome	**Group**	**Pre**	**Post**	**Interaction Effect**	**Group Effect**	**Time Effect**
SBP, mmHg	BCS CTL	125 (11.5) 128 (9.4)	122 (10.0) 125 (7.1)	0.812	0.436	0.068
DBP, mmHg	BCS CTL	79.2 (7.4) 79.3 (4.8)	76.6 (8.2) 78.3 (3.9)	0.582	0.635	0.164
MAP, mmHg	BCS CTL	93.4 (8.6) 94 (5.4)	90.1 (9.0) 92.7 (3.3)	0.474	0.509	0.066
HR, beats/min	BCS CTL	67 (10) 63 (11)	66 (13) 64 (11)	0.671	0.501	0.964
AIx, %	BCS CTL	26.7 (11.1) 28.4 (6.6)	25.0 (11.1) 29.4 (7.2)	0.390	0.345	0.951
cSBP, mmHg	BCS CTL	115 (11.3) 118 (8.8)	112 (10.0) 116 (6.3)	0.687	0.372	0.078
Buckberg	BCS CTL	145 (21.5) 144 (20.0)	148 (24.6) 146 (20.3)	0.800	0.799	0.440
Double Product, mmHg*bpm	BCS CTL	7687 (1377) 7392 (1188)	7402 (1645) 7358 (1140)	0.585	0.761	0.471

[+] adjusted for mean arterial pressure (MAP). Data represented as means (SD). BCS, breast cancer survivors, n=27; CTL, controls, n =10; PWV, pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; AIx, augmentation index; cSBP, central systolic blood pressure; BUCK, Buckberg Index.

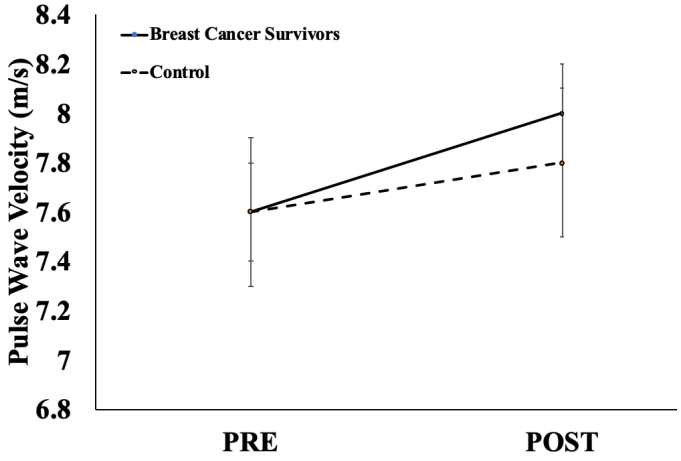


Figure 2 Arterial stiffness at baseline and following 16-weeks of community-based exercise (mean(SE) using estimated marginal means from MAP-adjusted linear mixed model).

Sensitivity analyses revealed no time x group interactions for PWV (Table 6) for either of the breast cancer treatment analyses or for menopausal status. A significant main effect for time demonstrated PWV in BCS significantly increased by 0.4m/s at post-test (95% CI [0.103, 0.781]; p=0.016) regardless chemotherapy status. For the radiation analysis, a significant main effect for group revealed PWV was higher at pre and post testing in women who received radiation (0.93 m/s; 95% CI [0.257, 1.607]; p=0.012) than those who did not, but a significant main effect for time showed both groups of survivors increased arterial stiffness by 0.6m/s (95% CI [0.200, 0.169]; p<0.01) after exercise training. Changes in arterial stiffness between pre and postmenopausal women were non-significant but demonstrated a medium effect size (Cohen's D= -0.46).

Table 6 Results from linear mixed model of pulse wave velocity after 16-weeks of community-based exercise training in BCS with differing treatment regimens

		Mean (SE)					
Outcome	Group	Pre	Post	Cohen's *d* ^	Interaction Effect	Group Effect	Time Effect
PWV, m/s	BCS + C BCS - C	7.7 (0.2) 7.4 (0.3)	8.0 (0.2) 8.0 (0.3)	-0.33	0.495	0.692	**0.016**
PWV, m/s	BCS + R BCS - R	7.8 (0.2) 6.7 (0.4)	8.2 (0.2) 7.5 (0.3)	-0.45	0.266	**0.012**	**0.009**
*__PWV, m/s__	Premeno BCS Postmeno BCS	7.6 (0.3) 7.6 (0.3)	7.7 (0.3) 8.2 (0.3)	0.45	0.079	0.576	0.055

*Adjusted for MAP and age. ^calculated using change scores
Data represented as estimated marginal means (SE) from MAP-adjusted linear mixed model. PWV, pulse wave velocity; BCS, breast cancer survivors; C, chemotherapy; R, radiation; BCS+C n=16 , BCS-C n=11; BCS+R n=21, BCS-R n=6; Premeno n=11 ; Postmeno n=16 .Bold indicates *P* value < 0.05.

We found no significant univariate associations between change in PWV (deltaPWV) and independent variables in the BCS group. Based on the similarity in cardiovascular profiles between groups, the dataset was pooled for exploratory univariate analysis and revealed

significant associations between deltaPWV and aCOMP (R=-0.343, ß= -0.029, p=0.038) (Table 7).

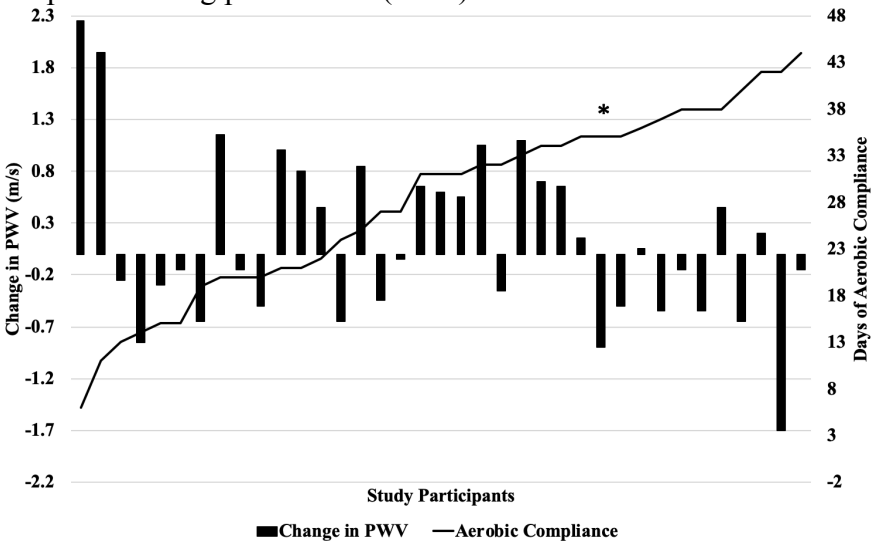
Table 7 Independent associations of change in pulse wave velocity (deltaPWV*) with baseline clinical measures and exercise engagement measures in the pooled sample (n=37)

	Univariate				
	R	**Beta**	**Lower 95% CI**	**Upper 95% CI**	***P value***
ATT^	-0.029	-0.003	-0.0351	0.0296	0.863
aCOMP^	-0.343	-0.029	-0.0564	-0.002	**0.038**
sCOMP^	-0.207	-0.0352	-0.0924	0.0219	0.219

Footnote: ATT=days of attendance to exercise intervention, aCOMP=days of aerobic exercise compliance, sCOMP= days of strength exercise compliance
^=higher values desired
*=lower values desired

While exploratory yet interesting, when graphed, relatively consistent improvement in arterial stiffness appears to occur following approximately 35 out of 48 days of aerobic compliant training (Figure 3). Six out of 11 (55%) participants had decreased PWV (3 (50%) of which were BCS), 3 (27%) were relatively unchanged, and 2 (18%) appeared to increase after 35 days (Figure 3).

Figure 3: Pre-post intervention change in PWV (deltaPWV, m/s) per days of aerobic exercise compliance using pooled data (n=37).



* = Denotes potential threshold for minimum number of days of aerobic compliance that appear to result in generally improved PWV

Discussion

Data, while limited, support arterial stiffness increases (>1m/s) during the first year of survivorship in BCS treated with cardiotoxic chemotherapy compared to non-cancer controls, and it is possible this deterioration in vascular-specific health may be a contributing factor to the increased cardiovascular risk profile of women with breast cancer (Chaosuwannakit et al., 2010; Drafts et al., 2013; L M Jones et al., 2013; Mulrooney et al., 2012). Arterial stiffness profile of patients treated with non-anthracycline therapies is not known. Two published studies support a potential beneficial role of exercise for vascular health in BCS but evaluated participants who were ~7 years post treatment (Lynnette M Jones et al., 2020; Koelwyn et al., 2016). Interestingly, in our study, baseline PWV for both BCS and CTL were lower compared to previous work (Chaosuwannakit et al., 2010; Drafts et al., 2013), lower than published reference values for non-cancer populations of similar age (Reference Values for Arterial Stiffness, 2010), and did not change following 16-weeks of exercise training when compared to CTL. However,

when evaluating changes in arterial stiffness in BCS only, significant increases in arterial stiffness were observed from pre to post testing regardless if women received chemotherapy ($p=0.016$) or radiation ($p<0.01$). Only two women in our BCS sample did not receive chemotherapy or radiation. Women treated with radiation also had greater arterial stiffness at pre-testing (1.15m/s, 95% CI [0.351, 1.95], $p<0.01$) than women who were radiation naïve. Regardless the absolute values of arterial stiffness at post-test still fall within healthy ranges, the change trajectory is not in a desired direction. Based on our findings in this exploratory subset analysis of BCS, chemotherapy and radiation may predispose survivors to increased arterial stiffness, and the impact of exercise on this change also warrants further investigation.

Based on our findings, progressive intensity exercise training may have little effect on arterial stiffness when comparing the cancer and non-cancer groups. It is possible that the exercise intervention may have prevented dramatic increases in arterial stiffness of our BCS like those observed in previously published cancer studies over similar time periods (Chaosuwannakit et al., 2010; Drafts et al., 2013). However, arterial stiffness still increased in BCS when evaluated independently, and it is not clear if this was influenced by cancer therapy alone, exercise participation, or both. This is difficult to resolve without a non-exercising breast cancer survivor group for comparison. Based on the cardiovascular measures collected in this study, our entire group of participants reflected healthy profiles which was somewhat unexpected, but the trajectory of change in arterial stiffness in an undesired direction (Chaosuwannakit et al., 2010; Drafts et al., 2013; Mulrooney et al., 2012). One question is whether the relatively healthy profile of our BCS will deteriorate over time similar to anthracycline-treated patients in pioneering publications (Chaosuwannakit et al., 2010; Drafts et al., 2013) or due menopausal changes (Yersal et al., 2018; Zagar et al., 2016) (as a medium

effect was observed for changes in PWV between our pre and postmenopausal BCS (Cohen's *d*=0.45, p=0.576)), or will be maintained as observed in other recent studies (Lynnette M Jones et al., 2019). Less than 20% of our sample was treated with anthracycline chemotherapy, unlike the participants included in founding studies, but stiffening trajectories still appear evident (Chaosuwannakit et al., 2010; Drafts et al., 2013; Koelwyn et al., 2016). These preliminary findings and the influence of exercise on their change deserve further investigation but reiterate existing literature that radiation and chemotherapy may contribute unique cardiovascular risk in BCS (Jain et al., 2017; Rygiel, 2017; Jessica M Scott et al., 2018; Zagar et al., 2016).

While exploratory, a very interesting finding of our study is the significant association between days of aerobic compliance and deltaPWV (R= -0.343, p=0.038) in the pooled dataset. We absolutely respect that a pooled dataset includes women with and without breast cancer, but this analysis was purely to explore potential associations between cardiovascular variables due to the nearly identical profile between BCS and CTL in this study. The significant relationship existed for aerobic compliance but not attendance (R=-0.029, p=0.863). Per the *a priori* definitions used in this study, compliance was innately dependent on attendance – one could not be compliant without attending a session. The lack of significant association between attendance and deltaPWV but the presence of a small but significant association between aerobic compliance and deltaPWV suggests exercise intensity may be a critical component when targeting vascular changes. These findings are congruent with results from a recent meta-analysis that supported aerobic exercise intensity as a significant correlate of improvements in arterial stiffness (Ashor et al., 2014). Exercise engagement at progressive intensity is something that is reasonably within an individual's control and with ~12% of the variation in deltaPWV attributed to days of aerobic exercise compliance per results of our study (R^2=0.117), the importance of

intensity should not be overlooked (Table 7). Furthermore, when presented graphically, (Figure 3) there appears to be a potential threshold where days of aerobic compliance achieved begin to demonstrate relatively consistent reduction in PWV from pre to post intervention. Although highly preliminary at this time, in our study, ≥35 of 48 prescribed days of compliant aerobic exercise appears to provide the greatest benefit in terms of arterial stiffness. A potential caveat however is that arterial stiffening was still observed when evaluating BCS as an independent group. At this time, it cannot be determined if progressive intensity exercise is beneficial or potentially harmful to arterial health in BCS. For future research about interventions to promote CV health in women with breast cancer, exercise training programs with progressive aerobic exercise intensity need further investigation. As a pooled group, it appears aerobic exercise intensity may benefit arterial stiffness but in BCS alone, arterial stiffness increased following exercise training. The true impact of exercise on arterial health in BCS, most of who received chemotherapy or radiation, cannot be clearly determined in this study.

Attendance, and compliance to exercise training programs are a well-recognized challenge in exercise oncology research (Amy A Kirkham et al., 2018; Neil-Sztramko, Winters-Stone, Bland, & Campbell, 2019). Attendance in the current study was moderate and similar to that of previously published projects, but compliance to the intervention prescription was sub-optimal (K S Courneya et al., 2007; Kerry S Courneya et al., 2013; Amy A Kirkham et al., 2018; van Waart et al., 2015). Based on the observations of our exercise staff and research team, participant compliance to training was primarily hindered by not reaching prescribed exercise intensity, as measured by self-reported RPE. This method has weakness of being a subjective measure; however, it is highly feasible in a community-based setting where heart rate monitors may be cumbersome and otherwise unrealistic. It was observed that while participants would and

could complete both prescribed duration (aerobic) and volume (sets x reps, strength) well, it was challenging for them to engage at prescribed intensity, especially in the second half of training when intensity targets increased. Strength training intensity was achieved less frequently than aerobic intensity for both groups, leading to fewer strength compliant days than aerobic (Table 6), which has been observed previously in this population (Amy A Kirkham et al., 2018; Ottenbacher et al., 2015; Santos et al., 2019). Training staff encouraged participants to safely reach the more difficult intensities and no adverse events were documented during training; therefore, lack of training support, injury, or unnecessary discomfort were unlikely contributors to sub-optimal intensity compliance. However, if increased aerobic compliance has the potential to improve arterial stiffness, as suggested by our study, determining how to successfully engage participants at increasing intensities should remain a priority for the benefit of cardiovascular health. This is particularly important in the long term as arterial stiffening and cardiovascular risk naturally increase with age, and the latter especially so in BCS (Grover et al., 2015; McEniery et al., 2005; Patnaik et al., 2011; Vaitkevicius et al., 1993)

The primary limitation of this study is that it is underpowered due to small sample size. Five participants in both the BCS and the CTL groups were not included in analysis due to inability to capture a clear pulse wave reading at pre-testing. Adiposity around the neck of these participants prevented detecting a clear signal and complicated the ability to capture vascular outcomes. Other techniques such as cuff-based capture instead of applanation tonometry for carotid pulse readings may be appropriate in individuals where higher body fat complicates readings. Another limitation of this study is self-selection as participants had to be relatively locally residing, willing, able, and interested in participating in a four-month training study. This may have unintentionally recruited “worried but well” survivors who may represent a slightly healthier

subsample compared to the general population of BC survivors. Participants were also mostly white and had the job and family flexibility to be able to participate in 3 day/week training. This profile may poorly represent the majority of survivors in the same time frame post primary cancer treatment and future work would benefit from the inclusion of more diverse participants.

In conclusion, while preliminary, our overall clinical findings are reassuring that early stage breast cancer survivors treated primarily with non-anthracycline therapies have similar and healthy cardiovascular profiles as age-matched, non-cancer counterparts before and after exercise training. However, exploratory analyses revealed arterial stiffness of BCS does appear to increase in those treated with chemotherapy or radiation following exercise. The preliminary nature of this investigation prevents our ability to conclude if exercise is beneficial or harmful in this patient population and deserves additional attention for clarification. In the long term, improving our understanding of how arterial health of BCS changes naturally and in response to exercise training will enhance our ability to properly advise patients regarding strategies to promote their cardiovascular health.

CHAPTER FIVE: MANUSCRIPT TWO

Background

Aerobic capacity reflects the ability to use oxygen to produce energy for physical work, is impaired in breast cancer survivors (BCS), and associated with all-cause mortality, morbidity and disease-specific mortality (Blair et al., 1989; L. W. Jones, Hornsby, et al., 2012; L. W. Jones et al., 2010; Lakoski et al., 2013; A. B. Peel, Thomas, Dittus, Jones, & Lakoski, 2014; J. B. Peel et al., 2009). Aerobic capacity diminishes on average 5-10% during treatment but as much as 20-30% by the end of treatment, which is the equivalent of approximately 10 years of age-related declines in VO_2 (K S Courneya et al., 2007; L. W. Jones, Courneya, et al., 2012). A single metabolic equivalent (MET) increase in aerobic capacity (3.5 mL/kg/min) corresponds with 12-15% reduction in all-cause mortality risk and increases in aerobic capacity are associated with reduced cardiovascular (CV) risk in cancer and non-cancer populations (Barlow et al., 2012; A A Kirkham et al., 2016; A A Kirkham & Davis, 2015; Kodama et al., 2009; Myers et al., 2002). This relationship is of particular importance in a patient population like BCS where CV disease is a leading cause of death (Patnaik et al., 2011). From a quality of life perspective, adequate aerobic capacity supports the ability to be physically functional and live independently which are critical components of long-term survivorship (Swartz et al., 2017). Therefore, maintaining or promoting aerobic capacity and physical function in survivorship is essential to breast cancer survivorship (Demark-Wahnefried, Morey, Sloane, Snyder, & Cohen, 2009).

Aerobic exercise has long been documented to improve aerobic capacity in non-cancer populations and is rapidly gaining appreciation in the exercise oncology arena (Battaglini et al., 2014b; Campbell et al., 2019; Hayes, Newton, Spence, & Galvão, 2019; A A Kirkham et al., 2016; Ozemek et al., 2018). In recent decades, the addition of resistance/strength training to aerobic exercise has increased and has proved beneficial for cancer survivors, especially in terms of muscular strength which is a well-recognized impairment in BCS (Battaglini et al., 2014b; Hanson, Wagoner, Anderson, & Battaglini, 2016). Multiple, well-designed and controlled exercise intervention trials have tested and demonstrated the beneficial impact of exercise on aerobic capacity in cancer survivors so that there is now strong evidence to support the recommendation of 2-3 days/week of moderate intensity aerobic and strength training exercise for approximately 12 weeks for improving physical function and aerobic capacity in cancer patients (Battaglini et al., 2014b; Campbell et al., 2019; McNeely et al., 2006). With the advent of increasingly specific exercise prescriptions, the translation of laboratory/research trial-based exercise interventions to "real-world" settings is now possible, but is yet to be well-studied. However, this is important to evaluate to establish potential effectiveness for survivors seeking exercise participation in practical venues (Amy A Kirkham et al., 2018).

Community-based exercise programs may provide more flexible and hence feasible options for survivor access, accommodation, and enjoyment, with the trade-off of less control over exercise fidelity compared to a lab-based setting. Community-based programs have the potential to play an important role in breast cancer survivorship, however, further work is needed to determine the efficacy of "trial-proven" prescriptions delivered through these real world settings in an environment where the survivorship pool is growing (Bluethmann et al., 2016; Swartz et al., 2017). The purpose of this study was to evaluate the impact of the Get REAL &

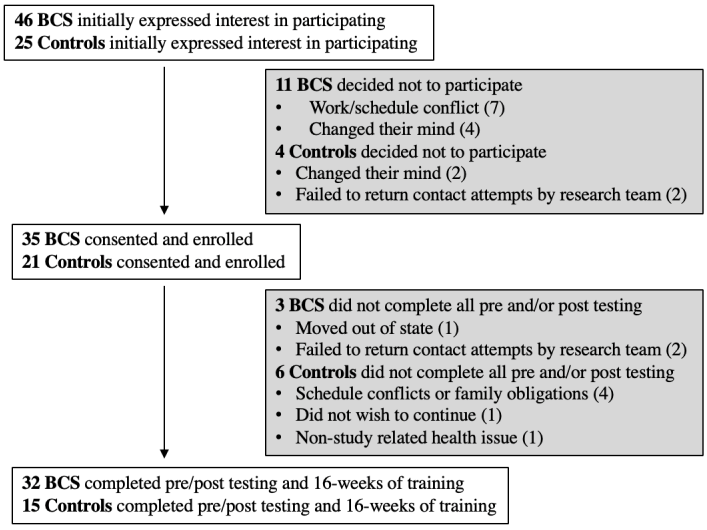
Heel Cancer & Exercise Program (GRH) on aerobic capacity of BCS in and around Chapel Hill, North Carolina. This established program has served cancer survivors since 2006 through small group exercise training that is highly reflective of current national physical activity guidelines for cancer survivors (Campbell et al., 2019). The program includes progressive intensity aerobic and strength exercise training for cancer survivors, 3 days per week for a 16-week series.

Methods

Study Overview

In this non-randomized study, two groups of women (one BCS, one non-cancer controls) of similar age and activity level were recruited (Figure 1). Women completed two days of exercise testing (pre) in a research laboratory and then asked to complete 16-weeks of exercise training at a local community-based program before repeating exercise testing (post). The study was approved by the Protocol Review Committee of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center and the Institutional Review Board of the Department of Exercise and Sport Science and School of Medicine at UNC Chapel Hill. All participants provided written informed consent.

Figure 1 Recruitment and retention



Study Participants

Breast cancer survivors had been diagnosed with early-stage (0-III) breast cancer and were within one year of completing primary therapy (chemotherapy, radiation, surgery) but could still be on endocrine therapy. Participants in the CTL group were age matched, did not have a history of cancer, and self-reported they were physically active no more than 2 days per week. Both groups were free from overt cardiovascular, metabolic, or orthopaedic limitations, and were cleared by cardiologists and oncologists (BCS only) prior to participating in the study. Participants in the BCS group were recruited through the Medical Oncology clinic at the North Carolina Cancer Hospital, and by word of mouth through local oncologists and cancer centers. Participants in the CTL group were residents from local cities including Raleigh, Durham, Chapel Hill and surrounding areas recruited via electronic and paper fliers and word of mouth.

Intervention

For both groups, the 16-week intervention entailed supervised, progressive, aerobic and strength exercise training (Table 1) at the UNC Get REAL & Heel Exercise Program, three days a week for approximately one hour per day. Participants were asked to maintain their current lifestyle habits outside of GRH training in order to best evaluate the program-specific effects. A variety of training equipment for both aerobic and resistance/strength has been used at GRH to adapt to individual participant fitness and mobility needs which allows trainers the ability to maximize patient safety and exercise engagement. For example, participants could choose treadmills, stationary bikes or ellipticals for aerobic work and dumbbells, resistance bands, or machine weights for strength training, depending on survivor ability and comfort. The specific prescription design used in the program and this study is presented in Table 1. Participants were encouraged to challenge themselves to safely engage at their prescribed workloads, with

increasing exercise intensity and duration/volume over time. The priority for training staff was to bring participants safely "up to speed" to attain weekly exercise goals reflective of current national guidelines (Campbell et al., 2019).

Table 1 Exercise progression in the Get REAL & Heel Exercise Program

AEROBIC EXERCISE		**WEEK 1-2**	**WEEK 3-7**	**WEEK 8-16**
• Treadmill • Stationary bike • Elliptical • Stepper	Duration (min)	10-15	10-30	30
	Intensity	Low		Moderate
	RPE	8-11		12-14
STRENGTH EXERCISE		**WEEK 1-2**	**WEEK 3-5**	**WEEK 5-16**
• Body weight • Resistance bands • Machine • Dumbbells	Duration (min)	30		
	Intensity	Light to moderate		High
	RPE	7-13		14-15
	Sets x Reps / exercise	1x15	2x10-15	2x10

Training records were used to track participant attendance and exercise compliance over 16 weeks. Attendance was calculated as the number of days participants came to the GRH facility. Aerobic compliance (aCOMP) was calculated as the number of days the participant achieved ≥80% of prescribed duration at the prescribed intensity using Borg Rating of Percieved Exertion (RPE) (Borg, 1973). Strength compliance (sCOMP) was calculated as the number of days the participants achieved ≥80% of prescribed strength volume (sets x reps) at the prescribed intensity using Borg RPE (Borg, 1973).

Overview of Procedures

All study participants completed two laboratory visits prior to (pre-intervention) and immediately following (post-intervention) the 16-week exercise program. Both sets of laboratory visits were conducted in the Exercise Oncology Research Laboratory (EORL) of the UNC Department of Exercise and Sport Science. On day one, participants completed a fasted body

composition assessment using Dual X-ray Absorptiometry (DEXA, Hologic (Discovery W) followed by one 6-minute walk test (6MWT) and two timed up-and-go (TUG) tests, with the fastest time recorded for analysis. Participants then completed a familiarization session for the cardiopulmonary exercise (CPET) testing using a Lode electronically-braked cycle ergometer. Participants were fitted to the bike and equipped with a Polar telemetry system (Polar Electro Inc., Lake Success, NY) to monitor heart rate and a gas exchange mask to measure the fit and function of ParvoMedics metabolic system, albeit no gas was collected or analyzed during familiarization. Participants completed a 5-minute unloaded and 20W loaded warm-up followed by an incremental 15 watt/minute with protocol up to 75% heart rate reserve for familiarization. To minimize the potential impact of learning effects on maximal testing and because many participants were likely unfamiliar with maximal exercise testing, familiarization was designed as an opportunity for participants to experience the general progression of the test protocol, become familiar and fitted with the required equipment, and increase their likelihood to engage at a true maximal effort on the testing day.

On day two, participants completed the same protocol but continued until they reached volitional exhaustion or were stopped when oxygen consumption plateaued despite increase in wattage, followed by lactate sampling at the fingertip 3 minutes post-test termination. Testing was also terminated if participants were unable to continue cycling exercising above 50rpm. Gas exchange was exported in five second average bins and peak oxygen consumption (VO_{2peak}) was recorded as the average of the three highest recordings within the final minute of the maximal test. Time to test termination (TTE) was recorded as the ramp-only portion which excluded the 5-minute warm up portion of the protocol, and peak wattage was the highest wattage recorded before test termination. Patient demographics and cancer-specific clinical data were extracted

from the UNC Health Care electronic medical record (EMR) by a member of the research team.

Power Calculations

Sample size estimates were calculated a priori and were based on the primary outcome, aerobic capacity. Published systematic reviews and meta analyses support exercise therapy to increase aerobic capacity in breast cancer survivors by approximately 2.3 - 2.8 mL/kg/min (Battaglini et al., 2014b; J M Scott et al., 2018). We opted for a change of 2.5mL/kg/min. The sample size required was 26 BCS and CTL participants total using magnitude-based inferences, but oversampling was performed to account for potential dropouts and missing data.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM, Armonk, NY) and jamovi open source computer software (The jamovi project, version 1.2.5) . Baseline descriptive statistics (means (SD); percentages for categorical variables) were computed to summarize participant demographics and breast cancer diagnosis/treatment characteristics at baseline (Table 2) and to summarize participant attendance and compliance with the exercise intervention (Table 3). Independent t-tests were used to compare groups at baseline, and to compare exercise attendance and compliance following training. Cohen's *d* was calculated for exercise attendance and compliance measures, using the difference between the outcome means for the BCS and CTL groups divided by the average pooled SD. For interpretation of effect sizes, Cohen's "rules of thumb" were used: small=0.20, medium=0.50, and large=0.80 (Cohen, 1977) .

Two linear mixed models were assessed in this study. The first evaluated the effects of time (pre vs. post) and group (BCS vs. CTL) on VO_{2peak}, BMI, body fat, peak power, relative peak power, peak RPE, peak HR, peak lactate, 6MWT, and TUG (Table 4). The second

evaluated the effects of time (pre vs. post) and cancer treatment group (BCS with chemo vs. BCS without chemo) on VO_{2peak} (Table 5). Both models used fixed effects of time and condition and a random effect of subject with adjustment for age. The a-level was set a priori for all statistical procedures at < 0.05. If time-by-condition interactions were not significant, the final models estimated the main effects of condition and time on all outcomes.

Because the purpose of this study was to evaluate the impact of community-based exercise training on aerobic capacity, univariate linear regression models were used to evaluate associations of pre-post change in VO_{2peak} (deltaVO_{2peak}, adjusted for age) with days since end of treatment (EOT), days of exercise attendance (ATT), days of aerobic exercise compliance (aCOMP), and days of strength exercise compliance (sCOMP) in the BCS group (Table 6). For exploratory purposes, univariate analyses were then repeated using the pooled sample (BCS plus CTL) (Table 7). Due to sample size limitations, multivariable analyses were not conducted.

Results

Thirty-five women with breast cancer were enrolled, of which 32 completed all pre and post intervention testing. Twenty-one non-cancer controls were enrolled, of which 15 completed all pre and post testing (Figure 1). Those who did not complete post testing were excluded due to missing data but otherwise very similar to women with complete data. At baseline (Table 2), groups differed by height (p=0.035), peak RPE (p=0.028), peak lactate (p=0.030), and TUG performance (p<0.01) but no differences were observed for aerobic capacity (VO_{2peak} (mL/kg/min), BCS: 20.9 (5.3) vs CTL: 22.4 (2.8), Cohen's *d*= 0.37, p=0.326).

Table 2 Baseline Characteristics of Breast Cancer and Control Groups presented as mean (SD)

	Total n=46	**Breast Cancer** n=31	**Control** n=15	**p-value**
Demographics				
Age (yr)	54 (11)	54 (12)	55 (8)	0.830
Height (cm)	165 (8)	167 (7)	162 (7)	**0.035**
Weight (kg)	76 (13)	77 (12)	75 (14)	0.758
BMI categories (kg/m^2)				
Normal (18.5 to < 25)	24%	29%	13%	0.215
Overweight (25 to <30)	52%	48%	60%	0.337
Obese (30 to <35)	9%	10%	7%	0.606
Obese II (≥35)	15%	13%	20%	0.411
Body Fat (%)	41 (5)	41 (6)	40 (4)	0.633
Lean mass (kg)	42 (6)	42 (6)	42 (7)	0.997
Postmenopausal (%)	65%	65%	67%	1.000
Race (Caucasian, %)	91%	87%	100%	0.288
Clinical Variables				
VO_{2peak} (mL/kg/min)	21.4 (4.6)	20.9 (5.3)	22.4 (2.8)	0.326
Time to Exertion (mm:ss)	9:54 (1:36)	9:41 (1:42)	10:21 (1:20)	0.186
Peak Power (Watt)	123 (24)	120 (26)	130 (20)	0.180
Relative Peak Power (Watt/kg)	1.6 (0.4)	1.6 (0.4)	1.8 (0.3)	0.214
Heart Rate Max (bpm)	160 (17)	160 (20)	159 (12)	0.814
Max RPE (Borg 6-20)	17 (2)	17 (2)	18 (1)	**0.028**
Lactate (mmol)	6.8 (1.9)	6.4 (1.9)	7.6 (1.6)	**0.030**
Six Minute Walk (m)	544 (67)	538 (72)	557 (53)	0.367
Timed Up & Go (sec)	4.5 (1.2)	4.8 (1.2)	3.9 (0.7)	**0.002**
Breast Cancer Details				
Tumor Stage				
0		3%		
I		27%		
II		47%		
III		23%		
HR Status				
ER Positive		81%		
HER2 Status				
Positive (all received Trastuzumab)		26%		
Surgery				
Lumpectomy		71%		
Mastectomy		29%		

Treatment Received			
Radiation		81%	
Chemotherapy		65%	
Cardiotoxic Therapies			
Anthracycline		23%	
Trastuzumab		26%	
Anthra + Tras		3%	
Endocrine Therapy			
Aromatase Inhibitor		45%	
Tamoxifen		19%	

Exercise attendance was similar between BCS and CTL groups with both groups attending approximately 71% of possible days of training (Table 3). Aerobic training prescription compliance differences between groups demonstrated a medium effect size (Cohen's *d*= 0.63) but was not statistically significant (p=0.06). Strength training prescription compliance, was significantly different between groups, with controls completing more compliant days of strength training compared to survivors (CTL 18 (3) days vs. BCS 14 (5) days); Cohen's *d*= 1.0, p=0.011) out of 48 total possible days.

Table 3 Attendance and Compliance (out of 48 total days of training opportunity)

	Breast Cancer mean (SD) n=31	**Control** mean (SD) n=15	**Cohen's *d* Effect Size**	**p-value**
Intervention Attendance (days)	35 (9)	33 (9)	0.22	0.420
Aerobic Compliance (days)	26 (10)	32 (9)	-0.63	0.060
Strength Compliance (days)	14 (5)	18 (3)	-1.00	**0.011**

There were no significant time x group interactions for VO_{2peak} but a significant main effect for time was observed with both groups improving aerobic capacity by approximately 1.2mL/kg/min (95% CI [0.15, 2.27]; p=0.03) from pre to post testing (Figure 2A). There was a significant time x group interaction for peak power (Figure 2B) with both groups demonstrating increased power but BCS increasing by approximately 10 more watts than CTL (95% CI

[1.8,17.5]; p=0.02) at post testing. A significant main effect of time was observed for 6MWT with both groups walking approximately 35 meters more (95% CI [21.5, 49.1]; p<0.001) and for time to exhaustion (Figure 2C) with both groups completing almost a minute more of exercise during their peak test (95% CI [0.60, 1.29]; p<0.001) at post testing. Significant main effects of time and group were observed for TUG with both groups improving their time by approximately 0.4 seconds (95% CI [-0.72, -0.17]; p<0.01) with a ~0.8 second difference between groups sustained after exercise training (95% CI [0.21, 1.5]; p=0.012). There were no significant time x condition interactions for VO_{2peak} or significant main effects of time or group between BCS who had chemotherapy and those who did not (Table 5).

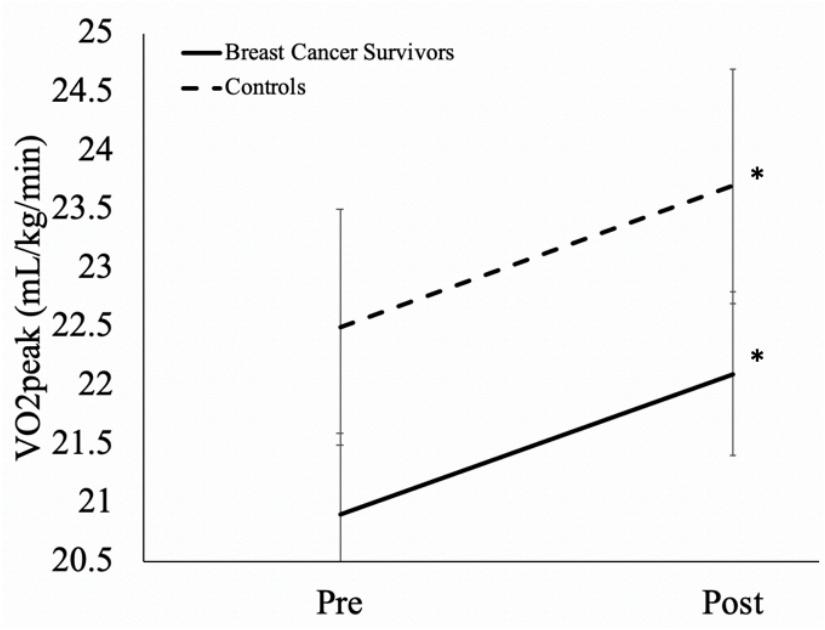
Table 4 Results from linear mixed model of cardiorespiratory fitness outcomes after 16-weeks of community-based exercise training in breast cancer survivors and non-cancer controls

		Mean (SD)					
Outcome	**Group**	**Pre**	**Post**	**Cohen's *d***	**Interaction Effect**	**Group Effect**	**Time Effect**
Body Fat, %	BCS CTL	40.7 (5.8) 39.9 (4.3)	40.5 (5.9) 39.8 (4.6)	0.04	0.901	0.651	0.668
Mass, kg	BCS CTL	76.7 (12.3) 75.5 (13.8)	76.8 (12.4) 74.7 (15.4)	-0.38	0.233	0.682	0.233
Time to Exhaustion, mm:ss	BCS CTL	9:41 (1:42) 10:24 (1:20)	10:48 (2:01) 11:06 (2:19)	0.30	0.345	0.374	**<0.001**
Peak Power, watts	BCS CTL	120 (25.6) 130 (20.1)	136 (30.1) 137 (21.7)	-0.76	**0.020**	0.493	**<0.001**
Peak RPE	BCS CTL	17 (2) 18 (1)	17 (2) 17 (2)	-0.51	0.114	0.122	0.083
Peak HR, bpm	BCS CTL	160 (20) 159 (12)	160 (17) 159 (14)	0.06	0.839	0.872	0.955
Peak Lactate, mmol	BCS CTL	6.4 (1.9) 7.6 (1.6)	7.4 (2.2) 7.7 (2.0)	-0.49	0.110	0.137	0.060
6MWT, m	BCS CTL	538 (72) 557 (54)	571 (77) 594 (35)	0.08	0.798	0.295	**<0.001**
TUG, sec	BCS CTL	4.8 (1.3) 3.9 (0.7)	4.3 (1.3) 3.6 (0.5)	0.27	0.399	**0.012**	**0.003**

*adjusted for age. Data represented as means (SD). BCS, breast cancer survivors, n=31; CTL, controls, n =15; PWV, pulse wave velocity; BMI, body mass index; HR, heart rate; RPE, rating of perceived exertion; 6MWT, 6-minute walk test; TUG, timed up & go.

Figure 2 Aerobic capacity (A); Peak wattage (B); Time to Exhaustion (C) of BCS and CTL before and after 16-weeks of training. *P<0.05 from baseline; ^P<0.001 from baseline, #P<0.05 interaction effect. Data for A are mean(SE) using estimated marginal means from adjusted model. Data for B and C are descriptive means, with standard deviation excluded for simplicity.

A



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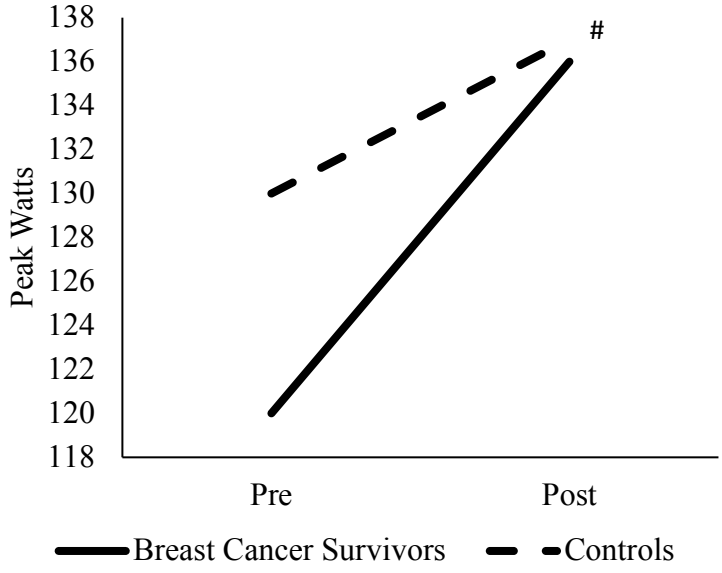

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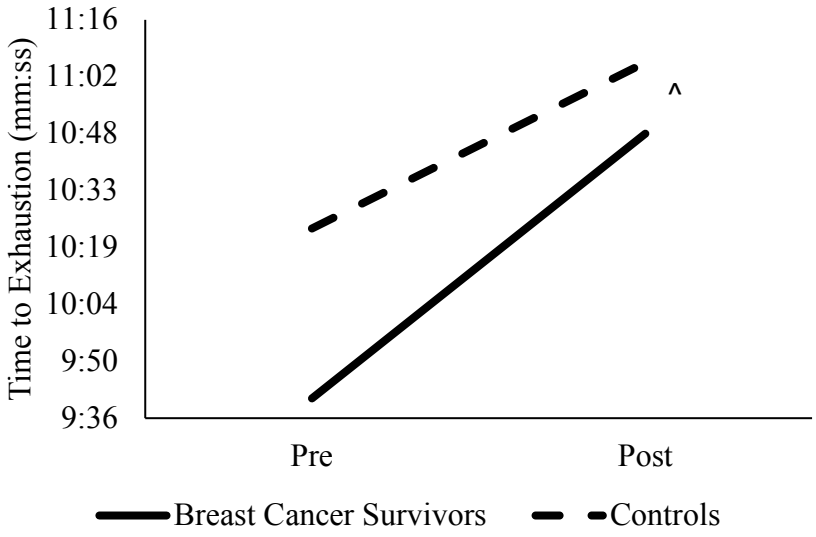

Table 5 Results from linear mixed model of aerobic capacity after 16-weeks of community-based exercise training in breast cancer survivors who did and did not receive chemotherapy

		Mean (SE)				
Outcome	**Group**	**Pre**	**Post**	**Interaction Effect**	**Group Effect**	**Time Effect**
***VO_{2peak}, mL/kg/min**	BCS + C BCS - C	20.9 (0.9) 21.0 (1.2)	22.3 (0.9) 22.0 (1.2)	0.713	0.940	0.070

*adjusted for age. Data represented as means (SE) using estimated means from age-adjusted linear mixed model. BCS + C, breast cancer survivors who received chemotherapy, n=16; BCS - C, breast cancer survivors who did not receive chemotherapy, n =11

There were no significant associations found in univariate analysis between deltaVO_{2peak} and selected study variables for either the BCS group alone (Table 6) or in the pooled sample (Table 7).

Table 6 Independent associations of age-adjusted change in aerobic capacity (deltaVO$_{2peak}$)^ with baseline clinical and cardiovascular measures in BCS (n=31)

	Univariate				
	R^2 (adj)	**Beta**	**Lower 95% CI**	**Upper 95% CI**	***P value***
EOT	0.251	0.007	-0.024	0.006	0.205
ATT^	0.013	0.044	-0.118	0.203	0.591
aCOMP^	0.021	0.070	-0.057	0.197	0.268
sCOMP^	0.005	0.107	-0.137	0.352	0.377

Footnote: EOT=Days since cancer treatment completion, ATT=days of attendance to exercise intervention, aCOMP=days of aerobic exercise compliance, sCOMP= days of strength exercise compliance
^=higher values desired

Table 7 Independent associations of age-adjusted change in aerobic capacity (deltaVO$_{2peak}$)^ with baseline clinical and cardiovascular measures in pooled sample (BCS + CTL, n=46)

	Univariate				
	R^2 (adj)	**Beta**	**Lower 95% CI**	**Upper 95% CI**	***P value***
ATT^	0.045	0.008	-0.033	0.199	0.157
aCOMP^	0.059	0.082	-0.019	0.183	0.107
sCOMP^	0.030	0.121	-0.089	0.331	0.252

Footnote: ATT=days of attendance to exercise intervention, aCOMP=days of aerobic exercise compliance, sCOMP= days of strength exercise compliance
^=higher values desired

Discussion

Aerobic capacities of BCS are known to diminish during breast cancer treatment and survivorship as a result of "multiple hits" from therapy and lifestyle changes (L. W. Jones, Haykowsky, Swartz, et al., 2007). Survivors may experience up to 20-30% loss during their cancer journey but trial-based exercise interventions of similar length/design as our study have proven effective in improving aerobic capacity by 2.3 – 2.8mL/kg/min (Battaglini et al., 2014b; J M Scott et al., 2018). As exercise intervention prescriptions have become more standardized (Campbell et al., 2019), it is important to determine if these prescriptions are still effective in improving aerobic capacity in real-world environments versus highly controlled lab settings.

Breast cancer survivors in our study had aerobic capacities (pre: 20.9 (5.3) mL O_2/kg/min, post: 22.2 (5.4) mL O_2/kg/min) that approximated published norms for survivors who

are post treatment (21.5 mL O_2/kg/min) (A. B. Peel et al., 2014). Aerobic capacities of our CTL participants were substantially lower than expected based on published norms from a meta-analysis (Fitzgerald, Tanaka, Tran, & Seals, 1997). However, the values for our sedentary CTL's are consistent with data on middle aged, sedentary women participating in other studies within our exercise lab in recent years and may potentially reflect a regional characteristic (Evans et al., 2015; Wagoner, Hanson, et al., 2019). The 1.2 mL/kg/min improvement in aerobic capacity in both groups following training is only approximately a 6% improvement from baseline and in BCS, did not differ in BCS with regard to chemotherapy. Training interventions similar to GRH are generally expected to elicit up to a 15% improvement in aerobic capacity in healthy populations (Warburton, Nicol, & Bredin, 2006a, 2006b). The change observed in our study is less than what is considered clinically significant in non-cancer populations (Kodama et al., 2009; Myers et al., 2002) and less than that observed in published meta-analyses where aerobic capacities of BCS increase by 2.3 – 2.5 mL/kg/min following training (Battaglini et al., 2014b; J M Scott et al., 2018). However, the improvements observed in our study are important as substantial cardiorespiratory fitness decline is a known manifestation of cancer survivorship and even small improvements can place survivors on a trajectory toward better health (L. W. Jones, Courneya, et al., 2012).

Both physical (aerobic) capacity and functional capacity (6MWT, TUG) improved in both groups following exercise training at our community-based center. Our survivors functional capacity improvements in 6MWT and TUG performance reflect improvements typical for BCS (Swartz et al., 2017) but are still not equivalent to non-cancer population norms (Rikli & Jones, 2013). Survivors and CTL groups also both increased the amount of time they could cycle on the bike at post-testing, indicating their stamina or ability to tolerate physical exertion for longer

time improved after exercise training. Collectively, these improvements support the benefits of modest exercise and have significant positive implications for tasks and demands of daily living.

Potential rationale for these findings primarily revolves around elements of exercise engagement. While attendance/adherence in our study (71%) is similar to previously published exercise oncology studies (~70-75%) (K S Courneya et al., 2007; Amy A Kirkham et al., 2018), it is important to recognize that that engagement (purely in relation to number of days/week compared to guidelines) only reflects what would be approximately 2/3 of national exercise oncology guidelines (Campbell et al., 2019). Moreover, strength compliance (sCOMP) in our study was particularly poor. It is logical to presume that improved exercise engagement closer to or matching recommended guidelines would lead to more or greater physiological changes. Difficulties with achieving exercise compliance, especially strength training, as observed in our study reflect the well-recognized challenges of exercise programming for clinical populations (K S Courneya et al., 2007; Kerry S Courneya et al., 2013; Amy A Kirkham et al., 2018; Neil-Sztramko et al., 2019; van Waart et al., 2015)

A limitation of our study but something that would help clarify our findings about the impact of the community-based training would be a third group of participants consisting of BCS who did not exercise for 16-weeks, or who completed prescriptions with differing levels of exercise volume (more days/reps/time) and/or differing intensity progression (higher vs lower intensity days). The CTL group in this study allowed us to compare exercise training equity between women who have been treated for cancer and women without a cancer/cancer treatment history, but does not provide insight to the natural fitness trajectory of BCS who do not exercise following treatment. When comparing absolute values of study outcomes between BCS and CTL groups, post-testing values for BCS tend to approximate pre-testing values for CTLs, as if they

are “catching up” to a more typical physical capacity profile of similarly-aged peers. Interestingly, improvements in peak power for BCS exceed the improvements in the CTL group, demonstrating a large effect size (Cohen’s *d*= -0.76). Peak lactate production also increases substantially in BCS from pre to post testing. Both of these changes result in post-testing values for BCS much like pre and post testing values for CTL and occur despite generally lower exercise compliance in the BCS group, but are positive nonetheless. It is unclear if these improvements in BCS are partially attributed simply to time since treatment completion plus exercise training, or if they truly respond differently to training stimuli than women without a cancer history. A third group of non-exercising BCS would very much improve the ability to compare natural versus training-induced changes. Other limitations to this study include relatively “self-selected” women who are mostly white, locally-residing, with the interest and job/family flexibility to be able to participate a 4-month training study. This likely does not reflect the majority of BCS. While it is well known that a survivor’s need to prioritize aspects of work, life and family balance around exercise participation can be a real challenge (Amy A Kirkham et al., 2018; Sweegers et al., 2018), future work would be improved by enrolling a more diverse pool of BCS for exercise training studies.

For the future, community-based programs like the UNC Get REAL & Heel Program will be essential for accommodating the growing number and needs of survivors for guideline-recommended exercise programs (Amy A Kirkham et al., 2018; Sweegers et al., 2019). While customization of exercise regimens as offered through the GRH program does not guarantee survivors will meet guidelines immediately, it may help facilitate the integration of exercise as a daily routine and is a first step to incorporating exercise as a life-long commitment. Furthermore, exercise facilities with proper programming and the capacity to customize both aerobic and

strength training may actually enhance or accelerate an individual's capacity to reach guidelines prescriptions due to ability to provide variety in modes or type of exercise. It will be important to continue evaluation of similar community-based programs to insure survivors have the best prescription progressions and participation opportunities to improve their health.

In conclusion, community-based exercise programs like the one used in our study show promise for improving both physical and functional capacity of BCS. Attention to strategies for improving both attendance and compliance to training protocols of increasing intensity, duration (aerobic training), and volume (strength training) will likely be important to maximize these outcomes. Providing cancer survivors with access to a physiologically beneficial and enjoyable exercise program like GRH cannot be overstated. Future efforts to create, operationalize, and continually evaluate community-focused exercise oncology programs has the potential to change the face of cancer care and maximize long term physical and functional outcomes for cancer survivors.

CHAPTER SIX: RESEARCH SYNTHESIS

Major Findings

Collectively, the findings from this study support the effectiveness of UNC's Get REAL & Heel community-based exercise program to improve physical and functional outcomes of women with early stage breast cancer when compared to age matched, non-cancer controls. From a research perspective, the findings provide critical physiological contributions to the exercise oncology arena and practical programming guides for the development of future interventions, studies, and facilities. However, from a humanistic point of view, these findings are not only positive, but almost celebratory. They provide long-awaited, scientifically-grounded confirmation that this program, which has operated for over a decade, can indeed provide the physical and functional benefits which survivors have consistently reported during participation, and for which the program was initially designed. The message of our data echoes the voices of GRH survivors. As a scientist and a physiologist, it is motivating to know we are able to provide those in need with an opportunity that can both *feel* and *be* beneficial. This critical component of our work and research is likely the most powerful take away, especially as it relates to dissemination and integration into standards of cancer care. The expansion and development of GRH type facilities to other locations will help provide more survivors with the opportunity to improve their health following a breast cancer diagnosis, but will require the support and approval of medical professionals.

Our breast cancer survivors clearly demonstrated impairments in aerobic capacity pre-intervention (preVO_{2peak}: 20.9 (5.3) which improved (postVO_{2peak}: 22.2 (5.4)) following modest participation in the exercise intervention, but still do not approximate that of age-similar non-cancer group norms. Survivors were also able to cycle longer, produce more power, walk farther in 6-minutes, and became more agile in the timed up-and-go after training. The implication of these benefits translating into practical daily life tasks such as self and family care, grocery shopping, household chores, and daily stamina are of utmost importance in this population. The differences between exercise attendance and compliance were not surprising, as they have been previously recognized in published work, but further support the notion that individualized programming and consistent communication with patients about benefits of both strength and aerobic exercise is likely necessary to reach training targets. Furthermore, it is hard to evaluate the impact of national guidelines delivered through real world settings on survivor outcomes when survivors are not fully meeting those recommendations.

In terms of aerobic capacity from a non-cancer perspective, a somewhat unexpected finding was the surprisingly low VO_{2peak} values of our non-cancer controls, and lack of improvement following training. While we have observed similar values for similar participant profiles in other studies of our lab, the potential that this may be a regional effect or characteristic is intriguing and worthy of further investigation. Regional dietary and lifestyle habits potentially reflective of unique cultural characteristics may predispose particular groups of people to poorer cardiovascular fitness which is important to know and manage for their own outcomes. However, also being able to identify these trends across larger subsets of people of different locations is important from research perspectives because those subsets are commonly used as “healthy” comparison groups to clinical populations. The differences between clinical

and control groups, and between geographical sites may be substantially divergent. These regional tendencies or characteristics will be very important to evaluate and balance, especially from an external validity point of view.

From a vascular outcomes perspective, our findings support the need for further investigation before conclusions can be confidently made. Between groups, arterial stiffness did not differ before or after exercise training. When groups were pooled for exploratory analysis, days of aerobic compliance appeared to benefit changes in arterial stiffness, suggesting exercise engagement may be a positive influence for vascular health. However, when exploring changes in the BCS group alone, arterial stiffness increased after exercise training in survivors treated with chemotherapy or radiation. The presence/absence and magnitude of change in arterial stiffness in patients primarily treated with non-anthracycline therapies is not currently known in the field. Therefore, it cannot be determined whether the observed increase in arterial stiffness of BCS in our study was potentially due to the effects of cancer therapies, was an increase potentially blunted by exercise, or was induced by exercise. It is imperative to determine these relationships especially as exercise is increasingly recommended for cancer survivorship. Patient-centered outcomes can absolutely be enhanced if we can better determine how to customize survivorship for women with different treatment histories.

The scientific contribution of this work is substantial from the perspective that the growing number of cancer survivors will soon challenge the capacities medical clinics are capable of providing. If community-based settings can help benefit health outcomes of survivors and support ways to keep or improve their ability to be physically self-sufficient and independent, this may alleviate some of the stress and demand on medical providers allowing those professionals more time to manage more difficult or acutely concerning cases. The obvious

overall challenge is actually getting additional programs like GRH off the ground and supporting their services long term, as well as having survivors successfully engage in exercise for the long term. Furthermore, ensuring the trainers and staff of those facilities are properly prepared to work with the unique needs of survivors is critical for safety and efficacy. Leveraging existing exercise facilities and established local cancer support groups/networks can help spearhead these efforts. While likely an arduous process, these goals should not be pushed aside.

Exploratory Findings

The exploratory analyses were significantly constrained by small sample size as they required participants having both useable PWV and VO_{2peak} values pre and post testing. There were 26 BCS and 10 CTL included for exploratory analysis. As previously mentioned, PWV was not captured on some individuals due to physical architecture challenges around the neck preventing a clear pulse wave reading.

The first exploratory analysis evaluated the relationship between pre-post change in aerobic capacity and baseline PWV, AIx, and Buckberg Index for each group. There were no significant associations found between deltaVO_{2peak} and any of the baseline outcomes for either group. The second exploratory analysis repeated exploratory aim one but further minimized sample size as each group (BCS and CTL) were each separated into 2 groups: responder (deltaVO_{2peak} $\geq$2.5mL/kg/min) or non-responder (deltaVO_{2peak} <2.5mL/kg/min). No significant associations were found between deltaVO_{2peak} and baseline outcomes for either response group in BCS or either response group in CTL.

The third exploratory analysis evaluated the relationship between baseline $p16^{INK4a}$ and deltaVO_{2peak} and baseline PWV, 6MWT, and lean body mass in BCS (n=25). No significant

associations were found and, while still under investigation by other groups, the clinical utility of $p16^{INK4a}$ has not yet been determined.

Strengths and Limitations

The greatest strength of this study was the ability to evaluate the effectiveness of a long-standing community-based program with a level of precision of an efficacy trial. Multiple gold-standard, well-controlled, lab-based outcomes were evaluated over consecutive time points. Participants were also able to participate in a well-oiled training program run by veteran training staff. This highly experienced environment was a great strength for our study but indeed a difficult combination to replicate, at least at this time when other community-based settings are sparse.

Significant limitations exist primarily regarding the population studied in this trial and an overall small sample size. Because of the 3-day/week training requirements, participants had to reside locally and/or have the interest and ability to travel to Chapel Hill three times per week. Overall, they also had to have the interest to exercise for four consecutive months. This made recruitment quite difficult and limited our sample size. Our population was a self-selected group which constrains the ability to extrapolate findings to women who may be less motivated or less able to attend sessions whether it be work, family, or transportation challenges among other things. For example, the majority of our participants were white, had decent flexibility around job demands (many retired or part time), and could manage family obligations which enabled them to participate in this study. We are well aware this profile is likely not the majority of women with breast cancer, especially those younger who may have more acute family and job demands. Improved race heterogeneity in a replica study would greatly benefit the capacity to evaluate training impact in a more representative population of breast cancer survivors.

Furthermore, if survivors are not motivated by involvement in a research trial, it may be quite difficult for survivors to prioritize exercise around other life-related challenges and exercise-induced benefits may subsequently change. Collectively, these weaknesses support the need for effective programming strategies to provide community-based facilities with flexible hours and a supportive training team to accommodate and encourage the best engagement possible.

Another limitation of our work revolves around the innate weakness of self-reported RPE as the gauge of exercise intensity in the training facility, however feasible and simple to use. Objective measures like heart rate can provide more specific, physiological based monitoring but can be challenging in a setting with limited number of trainers, and/or where smaller workout space may cause digital heart rate signals to overlap between participants and display incorrectly. However, exercise intensity is an important component to exercise progression. As our study suggests, specific health outcomes may be dependent on intensity engagement over time. Prescriptions are a known challenge when working with cancer survivors but using an RPE scale to monitor progression may be the most practical in our specific setting. Diligence to consistently re-contextualize patients to what the scale means and what represents their lowest and highest relative exertions can likely maximize the utility of this technique.

Future Research

From an outcome-specific perspective, a larger trial evaluating vascular health parameters at multiple time points in women treated with different types of chemotherapy and radiation regimens would be extremely helpful to profile the potential vascular threat of specific types and combinations of primary cancer treatment. Furthermore, evaluating the impact of exercise on these vascular profiles will help clarify is exercise is a safe and efficacious strategy to maintain or improve arterial health in BCS.

In conclusion, this study indeed supports the potential powerful role of community-based exercise training to benefit breast cancer survivors both physically and functionally, but more work is needed before concluding the impact of exercise on arterial health in BCS. More community-based programs are needed to serve the growing pool of survivors in general, and more programs that follow a consistent design reflective of ACSM exercise guidelines are essential to evaluate the efficacy of these national guidelines completed in a non-randomized controlled trial setting. Overall, the field faces the need for a volume of studies replicating the community-based design of our trial on physical and function outcomes and numerous studies to evaluate arterial health changes with and without exercise in survivors from diagnosis to beyond.

REFERENCES

19th WHO Model List of Essential Medicines (April 2015). (2015). Retrieved January 16, 2019, from https://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf

Adachi, K., Fujiura, Y., Mayumi, F., Nozuhara, A., Sugiu, Y., Sakanashi, T., … Toshima, H. (1993). A deletion of mitochondrial DNA in murine doxorubicin-induced cardiotoxicity. *Biochemical and Biophysical Research Communications*, *195*(2), 945–951. https://doi.org/10.1006/bbrc.1993.2135

Albini, A., Cesana, E., Donatelli, F., Cammarota, R., Bucci, E. O., Baravelli, M., … Noonan, D. M. (2011). Cardio-oncology in targeting the HER receptor family: the puzzle of different cardiotoxicities of HER2 inhibitors. *Future Cardiol*, *7*(5), 693–704. https://doi.org/10.2217/fca.11.54

Amir, E., Seruga, B., Niraula, S., Carlsson, L., & Ocana, A. (2011). Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *Journal of the National Cancer Institute*, *103*(17), 1299–1309. https://doi.org/10.1093/jnci/djr242

Armenian, S. H., Lacchetti, C., Barac, A., Carver, J., Constine, L. S., Denduluri, N., … Lenihan, D. (2017). Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*, *35*(8), 893–911. https://doi.org/10.1200/JCO.2016.70.5400

Ashley, N., & Poulton, J. (2009). Mitochondrial DNA is a direct target of anti-cancer anthracycline drugs. *Biochemical and Biophysical Research Communications*, *378*(3), 450–455. https://doi.org/10.1016/j.bbrc.2008.11.059

Ashor, A. W., Lara, J., Siervo, M., Celis-Morales, C., & Mathers, J. C. (2014). Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PloS One*, *9*(10), e110034. https://doi.org/10.1371/journal.pone.0110034

Barlow, C. E., Defina, L. F., Radford, N. B., Berry, J. D., Cooper, K. H., Haskell, W. L., … Lakoski, S. G. (2012). Cardiorespiratory fitness and long-term survival in "low-risk" adults. *Journal of the American Heart Association*, *1*(4), e001354. https://doi.org/10.1161/JAHA.112.001354

Barroco, A. C., Sperandio, P. A., Reis, M., Almeida, D. R., & Neder, J. A. (2017). A practical approach to assess leg muscle oxygenation during ramp-incremental cycle ergometry in heart failure. *Braz J Med Biol Res*, *50*(12), e6327. https://doi.org/10.1590/1414-431X20176327

Basch, E., Deal, A. M., Dueck, A. C., Scher, H. I., Kris, M. G., Hudis, C., & Schrag, D. (2017). Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA*, *318*(2), 197–198.

https://doi.org/10.1001/jama.2017.7156

Battaglini, C. L., Mills, R. C., Phillips, B. L., Lee, J. T., Story, C. E., Nascimento, M. G. B., & Hackney, A. C. (2014a). Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature. *World Journal of Clinical Oncology*, *5*(2). https://doi.org/10.5306/wjco.v5.i2.177

Battaglini, C. L., Mills, R. C., Phillips, B. L., Lee, J. T., Story, C. E., Nascimento, M. G., & Hackney, A. C. (2014b). Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature. *World J Clin Oncol*, *5*(2), 177–190. https://doi.org/10.5306/wjco.v5.i2.177

Beaudry, R. I., Howden, E. J., Foulkes, S., Bigaran, A., Claus, P., Haykowsky, M. J., & Gerche, A. La. (2019). Determinants of exercise intolerance in breast cancer patients prior to anthracycline chemotherapy. *Physiological Reports*, *7*(1), e13971. https://doi.org/10.14814/phy2.13971

Beaudry, R. I., Liang, Y., Boyton, S. T., Tucker, W. J., Brothers, R. M., Daniel, K. M., … Haykowsky, M. J. (2018). Meta-analysis of Exercise Training on Vascular Endothelial Function in Cancer Survivors. *Integrative Cancer Therapies*. https://doi.org/10.1177/1534735418756193

Benetos, A., Laurent, S., Hoeks, A. P., Boutouyrie, P. H., & Safar, M. E. (1993). Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arterioscler Thromb*, *13*(1), 90–97. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8422344

Bigby, J., & Holmes, M. D. (2005). Disparities across the breast cancer continuum. *Cancer Causes & Control : CCC*, *16*(1), 35–44. https://doi.org/10.1007/s10552-004-1263-1

Blaes, A., Beckwith, H., Florea, N., Hebbel, R., Solovey, A., Potter, D., … Duprez, D. (2017). Vascular function in breast cancer survivors on aromatase inhibitors: a pilot study. *Breast Cancer Res Treat*. https://doi.org/10.1007/s10549-017-4447-6

Blair, S. N., Kohl 3rd, H. W., Paffenbarger Jr., R. S., Clark, D. G., Cooper, K. H., & Gibbons, L. W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*, *262*(17), 2395–2401. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2795824

Bluethmann, S. M., Mariotto, A. B., & Rowland, J. H. (2016, July). Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*. United States. https://doi.org/10.1158/1055-9965.EPI-16-0133

Borg, G. A. (1973). Perceived exertion: a note on "history" and methods. *Medicine and Science in Sports*, *5*(2), 90–93. Retrieved from https://pubmed.ncbi.nlm.nih.gov/4721012

Boutouyrie, P., Laurent, S., Benetos, A., Girerd, X. J., Hoeks, A. P., & Safar, M. E. (1992).

Opposing effects of ageing on distal and proximal large arteries in hypertensives. *J Hypertens Suppl*, *10*(6), S87-91. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1432336

Brero, A., Ramella, R., Fitou, A., Dati, C., Alloatti, G., Gallo, M. P., & Levi, R. (2010). Neuregulin-1beta1 rapidly modulates nitric oxide synthesis and calcium handling in rat cardiomyocytes. *Cardiovasc Res*, *88*(3), 443–452. https://doi.org/10.1093/cvr/cvq238

Budinskaya, K., Puchnerova, V., Svacinova, J., Novak, J., Hrstkova, H., Novakova, M., … Novakova, Z. (2017). Non-invasive assessment of vascular system function and damage induced by anthracycline treatment in the pediatric cancer survivors. *Physiol Res*, *66*(Supplementum 4), S553–S560. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29355384

Bulten, B. F., Mavinkurve-Groothuis, A. M. C., de Geus-Oei, L.-F., de Haan, A. F. J., de Korte, C. L., Bellersen, L., … Kapusta, L. (2014). Early myocardial deformation abnormalities in breast cancer survivors. *Breast Cancer Research and Treatment*, *146*(1), 127–135. https://doi.org/10.1007/s10549-014-2997-4

Butlin, M., Qasem, A., Battista, F., Bozec, E., McEniery, C. M., Millet-Amaury, E., … Avolio, A. P. (2013). Carotid-femoral pulse wave velocity assessment using novel cuff-based techniques: comparison with tonometric measurement. *Journal of Hypertension*, *31*(11), 2237–2243; discussion 2243. https://doi.org/10.1097/HJH.0b013e328363c789

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *The New England Journal of Medicine*, *348*(17), 1625–1638. https://doi.org/10.1056/NEJMoa021423

Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., … Schmitz, K. H. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Medicine and Science in Sports and Exercise*, *51*(11), 2375–2390. https://doi.org/10.1249/MSS.0000000000002116

Cancer Statistics Center. (2018). 2019 Estimates. Retrieved from https://cancerstatisticscenter.cancer.org/?&_ga=2.10422647.356294908.1550923161-676593907.1550692051#!/

Chaosuwannakit, N., D'Agostino Jr., R., Hamilton, C. A., Lane, K. S., Ntim, W. O., Lawrence, J., … Hundley, W. G. (2010). Aortic stiffness increases upon receipt of anthracycline chemotherapy. *J Clin Oncol*, *28*(1), 166–172. https://doi.org/10.1200/JCO.2009.23.8527

Clarke, C. A., Purdie, D. M., & Glaser, S. L. (2006). Population attributable risk of breast cancer in white women associated with immediately modifiable risk factors. *BMC Cancer*, *6*, 170. https://doi.org/10.1186/1471-2407-6-170

Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans, V., … Early Breast Cancer Trialists' Collaborative, G. (2005). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, *366*(9503), 2087–2106. https://doi.org/10.1016/S0140-

6736(05)67887-7

Cohen, J. (1977). *Statistical power analysis for the behavioral sciences*. New York: Academic Press.

Courneya, K S, Mackey, J. R., Bell, G. J., Jones, L. W., Field, C. J., & Fairey, A. S. (2003). Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol*, *21*(9), 1660–1668. https://doi.org/10.1200/JCO.2003.04.093

Courneya, K S, Segal, R. J., Mackey, J. R., Gelmon, K., Reid, R. D., Friedenreich, C. M., … McKenzie, D. C. (2007). Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*, *25*(28), 4396–4404. https://doi.org/10.1200/JCO.2006.08.2024

Courneya, Kerry S, McKenzie, D. C., Mackey, J. R., Gelmon, K., Friedenreich, C. M., Yasui, Y., … Segal, R. J. (2013). Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *Journal of the National Cancer Institute*, *105*(23), 1821–1832. https://doi.org/10.1093/jnci/djt297

Courneya, Kerry S, Segal, R. J., McKenzie, D. C., Dong, H., Gelmon, K., Friedenreich, C. M., … Mackey, J. R. (2014). Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Medicine and Science in Sports and Exercise*, *46*(9), 1744–1751. https://doi.org/10.1249/MSS.0000000000000297

Coutinho, T., Turner, S. T., & Kullo, I. J. (2011). Aortic pulse wave velocity is associated with measures of subclinical target organ damage. *JACC. Cardiovascular Imaging*, *4*(7), 754–761. https://doi.org/10.1016/j.jcmg.2011.04.011

Cuzick, J., Stewart, H., Rutqvist, L., Houghton, J., Edwards, R., Redmond, C., … et al. (1994). Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol*, *12*(3), 447–453. https://doi.org/10.1200/JCO.1994.12.3.447

Darby, S. C., Ewertz, M., McGale, P., Bennet, A. M., Blom-Goldman, U., Bronnum, D., … Hall, P. (2013). Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*, *368*(11), 987–998. https://doi.org/10.1056/NEJMoa1209825

Davies, C., Pan, H., Godwin, J., Gray, R., Arriagada, R., Raina, V., … Adjuvant Tamoxifen: Longer Against Shorter Collaborative, G. (2013). Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*, *381*(9869), 805–816. https://doi.org/10.1016/S0140-6736(12)61963-1

Davies, J. I., & Struthers, A. D. (2003). Pulse wave analysis and pulse wave velocity: a critical review of their strengths and weaknesses. *J Hypertens*, *21*(3), 463–472. https://doi.org/10.1097/01.hjh.0000052468.40108.43

Demark-Wahnefried, W., Morey, M. C., Sloane, R., Snyder, D. C., & Cohen, H. J. (2009). Promoting healthy lifestyles in older cancer survivors to improve health and preserve

function. *Journal of the American Geriatrics Society*, *57 Suppl 2*, S262-4. https://doi.org/10.1111/j.1532-5415.2009.02507.x

DeMers D, W. D. (2019). Physiology, Mean Arterial Pressure. Retrieved January 25, 2020, from https://www.ncbi.nlm.nih.gov/books/NBK538226/%0A

DeSantis, C. E., Ma, J., Gaudet, M. M., Newman, L. A., Miller, K. D., Goding Sauer, A., … Siegel, R. L. (2019). Breast cancer statistics, 2019. *CA: A Cancer Journal for Clinicians*. https://doi.org/10.3322/caac.21583

Didier, K. D., Ederer, A. K., Reiter, L. K., Brown, M., Hardy, R., Caldwell, J., … Ade, C. J. (2017). Altered Blood Flow Response to Small Muscle Mass Exercise in Cancer Survivors Treated With Adjuvant Therapy. *J Am Heart Assoc*, *6*(2). https://doi.org/10.1161/JAHA.116.004784

Doroshow, J. H., Locker, G. Y., & Myers, C. E. (1980). Enzymatic defenses of the mouse heart against reactive oxygen metabolites: alterations produced by doxorubicin. *The Journal of Clinical Investigation*, *65*(1), 128–135. https://doi.org/10.1172/JCI109642

Dowsett, M., Cuzick, J., Ingle, J., Coates, A., Forbes, J., Bliss, J., … Peto, R. (2010). Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*, *28*(3), 509–518. https://doi.org/10.1200/JCO.2009.23.1274

Doyle, J. J., Neugut, A. I., Jacobson, J. S., Grann, V. R., & Hershman, D. L. (2005). Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol*, *23*(34), 8597–8605. https://doi.org/10.1200/JCO.2005.02.5841

Drafts, B. C., Twomley, K. M., D'Agostino Jr., R., Lawrence, J., Avis, N., Ellis, L. R., … Hundley, W. G. (2013). Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging*, *6*(8), 877–885. https://doi.org/10.1016/j.jcmg.2012.11.017

Early Breast Cancer Trialists' Collaborative, G., Darby, S., McGale, P., Correa, C., Taylor, C., Arriagada, R., … Peto, R. (2011). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*, *378*(9804), 1707–1716. https://doi.org/10.1016/S0140-6736(11)61629-2

Early Breast Cancer Trialists' Collaborative, G., Davies, C., Godwin, J., Gray, R., Clarke, M., Cutter, D., … Peto, R. (2011). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*, *378*(9793), 771–784. https://doi.org/10.1016/S0140-6736(11)60993-8

Ederer, A. K., Didier, K. D., Reiter, L. K., Brown, M., Hardy, R., Caldwell, J., … Ade, C. J. (2016). Influence of Adjuvant Therapy in Cancer Survivors on Endothelial Function and Skeletal Muscle Deoxygenation. *PLoS One*, *11*(1), e0147691. https://doi.org/10.1371/journal.pone.0147691

Erbel, R., Aboyans, V., Boileau, C., Bossone, E., Bartolomeo, R. D., Eggebrecht, H., …

Guidelines, E. S. C. C. for P. (2014). 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European . *Eur Heart J*, *35*(41), 2873–2926. https://doi.org/10.1093/eurheartj/ehu281

Evans, E. S., Hackney, A. C., McMurray, R. G., Randell, S. H., Muss, H. B., Deal, A. M., & Battaglini, C. L. (2015). Impact of Acute Intermittent Exercise on Natural Killer Cells in Breast Cancer Survivors. *Integr Cancer Ther*, *14*(5), 436–445. https://doi.org/10.1177/1534735415580681

Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. (2000). *Lancet*, *355*(9217), 1757–1770. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10832826

Felker, G. M., Thompson, R. E., Hare, J. M., Hruban, R. H., Clemetson, D. E., Howard, D. L., … Kasper, E. K. (2000). Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*, *342*(15), 1077–1084. https://doi.org/10.1056/NEJM200004133421502

Fitzgerald, M. D., Tanaka, H., Tran, Z. V, & Seals, D. R. (1997). Age-related declines in maximal aerobic capacity in regularly exercising vs. sedentary women: a meta-analysis. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *83*(1), 160–165. https://doi.org/10.1152/jappl.1997.83.1.160

Floyd, J. D., Nguyen, D. T., Lobins, R. L., Bashir, Q., Doll, D. C., & Perry, M. C. (2005). Cardiotoxicity of cancer therapy. *J Clin Oncol*, *23*(30), 7685–7696. https://doi.org/10.1200/jco.2005.08.789

Foglietta, J., Inno, A., de Iuliis, F., Sini, V., Duranti, S., Turazza, M., … Gori, S. (2017). Cardiotoxicity of Aromatase Inhibitors in Breast Cancer Patients. *Clinical Breast Cancer*, *17*(1), 11–17. https://doi.org/10.1016/j.clbc.2016.07.003

Foulkes, S. J., Howden, E. J., Bigaran, A., Janssens, K., Antill, Y., Loi, S., … LA Gerche, A. (2019). Persistent Impairment in Cardiopulmonary Fitness after Breast Cancer Chemotherapy. *Medicine and Science in Sports and Exercise*, *51*(8), 1573–1581. https://doi.org/10.1249/MSS.0000000000001970

Galimberti, V., Cole, B. F., Zurrida, S., Viale, G., Luini, A., Veronesi, P., … International Breast Cancer Study Group Trial, investigators. (2013). Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*, *14*(4), 297–305. https://doi.org/10.1016/S1470-2045(13)70035-4

Gernaat, S. A. M., Ho, P. J., Rijnberg, N., Emaus, M. J., Baak, L. M., Hartman, M., … Verkooijen, H. M. (2017). Risk of death from cardiovascular disease following breast cancer: a systematic review. *Breast Cancer Res Treat*, *164*(3), 537–555. https://doi.org/10.1007/s10549-017-4282-9

Giordano, S. H., Kuo, Y. F., Freeman, J. L., Buchholz, T. A., Hortobagyi, G. N., & Goodwin, J. S. (2005). Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst*, *97*(6), 419–424. https://doi.org/10.1093/jnci/dji067

Giordano, S. H., Lin, Y. L., Kuo, Y. F., Hortobagyi, G. N., & Goodwin, J. S. (2012). Decline in the use of anthracyclines for breast cancer. *J Clin Oncol*, *30*(18), 2232–2239. https://doi.org/10.1200/JCO.2011.40.1273

Gobel, F. L., Norstrom, L. A., Nelson, R. R., Jorgensen, C. R., & Wang, Y. (1978). The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation*, *57*(3), 549–556. https://doi.org/10.1161/01.cir.57.3.549

Gotzmann, M., Hogeweg, M., Seibert, F. S., Rohn, B. J., Bergbauer, M., Babel, N., … Westhoff, T. H. (2019). Accuracy of fully automated oscillometric central aortic blood pressure measurement techniques. *Journal of Hypertension*. https://doi.org/10.1097/HJH.0000000000002237

Gradishar, W. J., Anderson, B. O., Balassanian, R., Blair, S. L., Burstein, H. J., Cyr, A., … Shead, D. A. (2018). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*, *16*(3), 310–320. https://doi.org/10.6004/jnccn.2018.0012

Green, D J, Spence, A., Halliwill, J. R., Cable, N. T., & Thijssen, D. H. (2011). Exercise and vascular adaptation in asymptomatic humans. *Exp Physiol*, *96*(2), 57–70. https://doi.org/10.1113/expphysiol.2009.048694

Green, D J, Spence, A., Rowley, N., Thijssen, D. H., & Naylor, L. H. (2012). Vascular adaptation in athletes: is there an "athlete's artery"? *Exp Physiol*, *97*(3), 295–304. https://doi.org/10.1113/expphysiol.2011.058826

Green, Daniel J, Hopman, M. T. E., Padilla, J., Laughlin, M. H., & Thijssen, D. H. J. (2017). Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. *Physiological Reviews*, *97*(2), 495–528. https://doi.org/10.1152/physrev.00014.2016

Green, Daniel J, Maiorana, A., O'Driscoll, G., & Taylor, R. (2004). Effect of exercise training on endothelium-derived nitric oxide function in humans. *The Journal of Physiology*, *561*(Pt 1), 1–25. https://doi.org/10.1113/jphysiol.2004.068197

Green, Daniel J, & Smith, K. J. (2018). Effects of Exercise on Vascular Function, Structure, and Health in Humans. *Cold Spring Harbor Perspectives in Medicine*, *8*(4). https://doi.org/10.1101/cshperspect.a029819

Grover, S., Lou, P. W., Bradbrook, C., Cheong, K., Kotasek, D., Leong, D. P., … Selvanayagam, J. B. (2015). Early and late changes in markers of aortic stiffness with breast cancer therapy. *Intern Med J*, *45*(2), 140–147. https://doi.org/10.1111/imj.12645

Guerin, A. P., Blacher, J., Pannier, B., Marchais, S. J., Safar, M. E., & London, G. M. (2001). Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation*, *103*(7), 987–992. https://doi.org/10.1161/01.cir.103.7.987

Gyenes, G., Fornander, T., Carlens, P., Glas, U., & Rutqvist, L. E. (1996). Myocardial damage in breast cancer patients treated with adjuvant radiotherapy: a prospective study. *Int J Radiat Oncol Biol Phys*, *36*(4), 899–905. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8960519

Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell*, *100*(1), 57–70. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10647931

Hanson, E. D., Wagoner, C. W., Anderson, T., & Battaglini, C. L. (2016). The Independent Effects of Strength Training in Cancer Survivors: a Systematic Review. *Curr Oncol Rep*, *18*(5), 31. https://doi.org/10.1007/s11912-016-0511-3

Harris, E. E., Correa, C., Hwang, W. T., Liao, J., Litt, H. I., Ferrari, V. A., & Solin, L. J. (2006). Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. *J Clin Oncol*, *24*(25), 4100–4106. https://doi.org/10.1200/JCO.2005.05.1037

Hayes, S. C., Newton, R. U., Spence, R. R., & Galvão, D. A. (2019). The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. *Journal of Science and Medicine in Sport*, *22*(11), 1175–1199. https://doi.org/10.1016/j.jsams.2019.05.003

Henriksen, P. A. (2018). Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. *Heart (British Cardiac Society)*, *104*(12), 971–977. https://doi.org/10.1136/heartjnl-2017-312103

Herrero, F., Balmer, J., San Juan, A. F., Foster, C., Fleck, S. J., Perez, M., … Lucia, A. (2006). Is cardiorespiratory fitness related to quality of life in survivors of breast cancer? *Journal of Strength and Conditioning Research*, *20*(3), 535–540.

Hershman, D. L., Shao, T., Kushi, L. H., Buono, D., Tsai, W. Y., Fehrenbacher, L., … Neugut, A. I. (2011). Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Research and Treatment*, *126*(2), 529–537. https://doi.org/10.1007/s10549-010-1132-4

Hoffman, J. I., & Buckberg, G. D. (2014). The myocardial oxygen supply:demand index revisited. *J Am Heart Assoc*, *3*(1), e000285. https://doi.org/10.1161/JAHA.113.000285

Hooning, M. J., Botma, A., Aleman, B. M., Baaijens, M. H., Bartelink, H., Klijn, J. G., … van Leeuwen, F. E. (2007). Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*, *99*(5), 365–375. https://doi.org/10.1093/jnci/djk064

Hoppeler, H., & Weibel, E. R. (1998). Limits for oxygen and substrate transport in mammals. *The Journal of Experimental Biology*, *201*(Pt 8), 1051–1064.

Hull, M. C., Morris, C. G., Pepine, C. J., & Mendenhall, N. P. (2003). Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *JAMA*, *290*(21), 2831–2837. https://doi.org/10.1001/jama.290.21.2831

Hundley, W. G., Kitzman, D. W., Morgan, T. M., Hamilton, C. A., Darty, S. N., Stewart, K. P., … Little, W. C. (2001). Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *Journal of the American College of Cardiology*, *38*(3), 796–802.

Hwang, M. H., Yoo, J. K., Kim, H. K., Hwang, C. L., Mackay, K., Hemstreet, O., … Christou, D. D. (2014). Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. *Journal of Human Hypertension*, *28*(8), 475–481. https://doi.org/10.1038/jhh.2013.144

Irwin, M. L., Crumley, D., McTiernan, A., Bernstein, L., Baumgartner, R., Gilliland, F. D., … Ballard-Barbash, R. (2003). Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer*, *97*(7), 1746–1757. https://doi.org/10.1002/cncr.11227

Jain, D., Russell, R. R., Schwartz, R. G., Panjrath, G. S., & Aronow, W. (2017). Cardiac Complications of Cancer Therapy: Pathophysiology, Identification, Prevention, Treatment, and Future Directions. *Curr Cardiol Rep*, *19*(5), 36. https://doi.org/10.1007/s11886-017-0846-x

Jeukendrup, A., & Gleeson, M. (2018). Normal Ranges of Body Weight and Body Fat. In *Sport Nutrition* (3rd ed.). Human Kinetics. Retrieved from https://us.humankinetics.com/blogs/excerpt/normal-ranges-of-body-weight-and-body-fat

Jones, L. W., Courneya, K. S., Mackey, J. R., Muss, H. B., Pituskin, E. N., Scott, J. M., … Haykowsky, M. (2012). Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol*, *30*(20), 2530–2537. https://doi.org/10.1200/JCO.2011.39.9014

Jones, L. W., Eves, N. D., Peterson, B. L., Garst, J., Crawford, J., West, M. J., … Douglas, P. S. (2008). Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. *Cancer*, *113*(12), 3430–3439. https://doi.org/10.1002/cncr.23967

Jones, L. W., Habel, L. A., Weltzien, E., Castillo, A., Gupta, D., Kroenke, C. H., … Caan, B. J. (2016). Exercise and Risk of Cardiovascular Events in Women With Nonmetastatic Breast Cancer. *J Clin Oncol*, *34*(23), 2743–2749. https://doi.org/10.1200/JCO.2015.65.6603

Jones, L. W., Haykowsky, M. J., Swartz, J. J., Douglas, P. S., & Mackey, J. R. (2007). Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol*, *50*(15), 1435–1441. https://doi.org/10.1016/j.jacc.2007.06.037

Jones, L. W., Haykowsky, M., Pituskin, E. N., Jendzjowsky, N. G., Tomczak, C. R., Haennel, R. G., & Mackey, J. R. (2007a). Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor--positive operable breast cancer. *Oncologist*, *12*(10), 1156–1164. https://doi.org/10.1634/theoncologist.12-10-1156

Jones, L. W., Haykowsky, M., Pituskin, E. N., Jendzjowsky, N. G., Tomczak, C. R., Haennel, R. G., & Mackey, J. R. (2007b). Cardiovascular reserve and risk profile of postmenopausal

women after chemoendocrine therapy for hormone receptor--positive operable breast cancer. *Oncologist*, *12*(10), 1156–1164. https://doi.org/10.1634/theoncologist.12-10-1156

Jones, L. W., Hornsby, W. E., Goetzinger, A., Forbes, L. M., Sherrard, E. L., Quist, M., … Abernethy, A. P. (2012). Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer*, *76*(2), 248–252. https://doi.org/10.1016/j.lungcan.2011.10.009

Jones, L. W., Watson, D., Herndon 2nd, J. E., Eves, N. D., Haithcock, B. E., Loewen, G., & Kohman, L. (2010). Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer*, *116*(20), 4825–4832. https://doi.org/10.1002/cncr.25396

Jones, L M, Stoner, L., Brown, C., Baldi, C., & McLaren, B. (2013). Cardiovascular disease among breast cancer survivors: the call for a clinical vascular health toolbox. *Breast Cancer Res Treat*, *142*(3), 645–653. https://doi.org/10.1007/s10549-013-2766-9

Jones, Lynnette M, Stoner, L., Baldi, J. C., & McLaren, B. (2020). Circuit resistance training and cardiovascular health in breast cancer survivors. *European Journal of Cancer Care*, e13231–e13231. https://doi.org/10.1111/ecc.13231

Jones, Lynnette M, Stoner, L., Brown, C., Baldi, J. C., & McLaren, B. (2019). Cardiorespiratory fitness predicts cardiovascular health in breast cancer survivors, independent of body composition, age and time post-treatment completion. *Breast Cancer (Tokyo, Japan)*. https://doi.org/10.1007/s12282-019-00975-2

Kalin, M. F., & Zumoff, B. (1990). Sex hormones and coronary disease: a review of the clinical studies. *Steroids*, *55*(8), 330–352.

Kaminsky, L. A., Arena, R., Beckie, T. M., Brubaker, P. H., Church, T. S., Forman, D. E., … Metabolism. (2013). The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. *Circulation*, *127*(5), 652–662. https://doi.org/10.1161/CIR.0b013e31827ee100

Kass, D. A. (2005). Ventricular arterial stiffening: integrating the pathophysiology. *Hypertension (Dallas, Tex. : 1979)*, *46*(1), 185–193. https://doi.org/10.1161/01.HYP.0000168053.34306.d4

Kavanagh, T. (1983). Exercise and the heart. *Annals of the Academy of Medicine, Singapore*, *12*(3), 331–337.

Kavanagh, Terence, Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., & Shephard, R. J. (2003). Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *Journal of the American College of Cardiology*, *42*(12), 2139–2143.

Kearney, M. C., Gallop-Evans, E., Cockcroft, J. R., Stohr, E. J., Lee, E., Backx, K., … Shave, R. (2017). Cardiac dysfunction in cancer survivors unmasked during exercise. *Eur J Clin Invest*, *47*(3), 213–220. https://doi.org/10.1111/eci.12720

Khouri, M. G., Douglas, P. S., Mackey, J. R., Martin, M., Scott, J. M., Scherrer-Crosbie, M., & Jones, L. W. (2012). Cancer therapy-induced cardiac toxicity in early breast cancer:

addressing the unresolved issues. *Circulation*, *126*(23), 2749–2763. https://doi.org/10.1161/CIRCULATIONAHA.112.100560

Kilicaslan, B., Piskin, G. D., Susam, I., Dursun, H., & Ozdogan, O. (2014). Effect of radiotheraphy on impaired aortic elasticity and stiffness in patients with breast cancer. *Angiology*, *65*(7), 643–648. https://doi.org/10.1177/0003319713494463

Kim, D. H., & Braam, B. (2013). Assessment of arterial stiffness using applanation tonometry. *Canadian Journal of Physiology and Pharmacology*, *91*(12), 999–1008. https://doi.org/10.1139/cjpp-2013-0010

Kirkham, A A, Bland, K. A., Sayyari, S., Campbell, K. L., & Davis, M. K. (2016). Clinically Relevant Physical Benefits of Exercise Interventions in Breast Cancer Survivors. *Curr Oncol Rep*, *18*(2), 12. https://doi.org/10.1007/s11912-015-0496-3

Kirkham, A A, & Davis, M. K. (2015). Exercise Prevention of Cardiovascular Disease in Breast Cancer Survivors. *J Oncol*, *2015*, 917606. https://doi.org/10.1155/2015/917606

Kirkham, Amy A, Bonsignore, A., Bland, K. A., McKenzie, D. C., Gelmon, K. A., VAN Patten, C. L., & Campbell, K. L. (2018). Exercise Prescription and Adherence for Breast Cancer: One Size Does Not FITT All. *Medicine and Science in Sports and Exercise*, *50*(2), 177–186. https://doi.org/10.1249/MSS.0000000000001446

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., … Sone, H. (2009, May 20). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2009.681

Koelwyn, G. J., Khouri, M., Mackey, J. R., Douglas, P. S., & Jones, L. W. (2012). Running on empty: cardiovascular reserve capacity and late effects of therapy in cancer survivorship. *J Clin Oncol*, *30*(36), 4458–4461. https://doi.org/10.1200/JCO.2012.44.0891

Koelwyn, G. J., Lewis, N. C., Ellard, S. L., Jones, L. W., Gelinas, J. C., Rolf, J. D., … Eves, N. D. (2016). Ventricular-Arterial Coupling in Breast Cancer Patients After Treatment With Anthracycline-Containing Adjuvant Chemotherapy. *Oncologist*, *21*(2), 141–149. https://doi.org/10.1634/theoncologist.2015-0352

Kutynec, C. L., McCargar, L., Barr, S. I., & Hislop, T. G. (1999). Energy balance in women with breast cancer during adjuvant treatment. *Journal of the American Dietetic Association*, *99*(10), 1222–1227.

Kwan, M. L., Sternfeld, B., Ergas, I. J., Timperi, A. W., Roh, J. M., Hong, C.-C., … Kushi, L. H. (2012). Change in physical activity during active treatment in a prospective study of breast cancer survivors. *Breast Cancer Research and Treatment*, *131*(2), 679–690. https://doi.org/10.1007/s10549-011-1788-4

Lakoski, S. G., Barlow, C. E., Koelwyn, G. J., Hornsby, W. E., Hernandez, J., Defina, L. F., … Jones, L. W. (2013). The influence of adjuvant therapy on cardiorespiratory fitness in early-stage breast cancer seven years after diagnosis: the Cooper Center Longitudinal Study.

Breast Cancer Res Treat, *138*(3), 909–916. https://doi.org/10.1007/s10549-013-2478-1

Lakoski, S. G., Eves, N. D., Douglas, P. S., & Jones, L. W. (2012). Exercise rehabilitation in patients with cancer. *Nat Rev Clin Oncol*, *9*(5), 288–296. https://doi.org/10.1038/nrclinonc.2012.27

Lakoski, S. G., Jones, L. W., Krone, R. J., Stein, P. K., & Scott, J. M. (2015). Autonomic dysfunction in early breast cancer: Incidence, clinical importance, and underlying mechanisms. *Am Heart J*, *170*(2), 231–241. https://doi.org/10.1016/j.ahj.2015.05.014

Lanfranconi, F., Pollastri, L., Ferri, A., Fraschini, D., Masera, G., & Miserocchi, G. (2014). Near infrared spectroscopy (NIRS) as a new non-invasive tool to detect oxidative skeletal muscle impairment in children survived to acute lymphoblastic leukaemia. *PLoS One*, *9*(6), e99282. https://doi.org/10.1371/journal.pone.0099282

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., … Benetos, A. (2001). Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*, *37*(5), 1236–1241. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11358934

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., … European Network for Non-invasive Investigation of Large, A. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*, *27*(21), 2588–2605. https://doi.org/10.1093/eurheartj/ehl254

Laurent, S., Katsahian, S., Fassot, C., Tropeano, A. I., Gautier, I., Laloux, B., & Boutouyrie, P. (2003). Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke*, *34*(5), 1203–1206. https://doi.org/10.1161/01.STR.0000065428.03209.64

Layec, G., Trinity, J. D., Hart, C. R., Le Fur, Y., Sorensen, J. R., Jeong, E. K., & Richardson, R. S. (2016). Evidence of a metabolic reserve in the skeletal muscle of elderly people. *Aging (Albany NY)*, *9*(1), 52–67. https://doi.org/10.18632/aging.101079

Lebrecht, D, Geist, A., Ketelsen, U.-P., Haberstroh, J., Setzer, B., & Walker, U. A. (2007). Dexrazoxane prevents doxorubicin-induced long-term cardiotoxicity and protects myocardial mitochondria from genetic and functional lesions in rats. *British Journal of Pharmacology*, *151*(6), 771–778. https://doi.org/10.1038/sj.bjp.0707294

Lebrecht, Dirk, Kokkori, A., Ketelsen, U.-P., Setzer, B., & Walker, U. A. (2005). Tissue-specific mtDNA lesions and radical-associated mitochondrial dysfunction in human hearts exposed to doxorubicin. *The Journal of Pathology*, *207*(4), 436–444. https://doi.org/10.1002/path.1863

Lee, K. F., Simon, H., Chen, H., Bates, B., Hung, M. C., & Hauser, C. (1995). Requirement for neuregulin receptor erbB2 in neural and cardiac development. *Nature*, *378*(6555), 394–398. https://doi.org/10.1038/378394a0

Leening, M. J. G., Ferket, B. S., Steyerberg, E. W., Kavousi, M., Deckers, J. W., Nieboer, D., … Roos-Hesselink, J. W. (2014). Sex differences in lifetime risk and first manifestation of

cardiovascular disease: prospective population based cohort study. *BMJ : British Medical Journal*, *349*, g5992. https://doi.org/10.1136/bmj.g5992

Lichter, A. S., Lippman, M. E., Danforth Jr., D. N., d'Angelo, T., Steinberg, S. M., deMoss, E., … et al. (1992). Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. *J Clin Oncol*, *10*(6), 976–983. https://doi.org/10.1200/JCO.1992.10.6.976

Liu, C.-Y., Chen, D., Teixido-Tura, G., Chugh, A. R., Redheuil, A., Gomes, A. S., … Lima, J. A. (2012). Aortic size, distensibility, and pulse wave velocity changes with aging: longitudinal analysis from Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of Cardiovascular Magnetic Resonance*, *14*(Suppl 1), P126–P126. https://doi.org/10.1186/1532-429X-14-S1-P126

Liu, Y., Sanoff, H. K., Cho, H., Burd, C. E., Torrice, C., Ibrahim, J. G., … Sharpless, N. E. (2009). Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell*, *8*(4), 439–448. https://doi.org/10.1111/j.1474-9726.2009.00489.x

Lucero, A. A., Addae, G., Lawrence, W., Neway, B., Credeur, D. P., Faulkner, J., … Stoner, L. (2018). Reliability of muscle blood flow and oxygen consumption response from exercise using near-infrared spectroscopy. *Experimental Physiology*, *103*(1), 90–100. https://doi.org/10.1113/EP086537

Mancini, D. M., Bolinger, L., Li, H., Kendrick, K., Chance, B., & Wilson, J. R. (1994). Validation of near-infrared spectroscopy in humans. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *77*(6), 2740–2747. https://doi.org/10.1152/jappl.1994.77.6.2740

Mannion, T., Devaney, L., Fall, S., Carey, M., Jago, A., Fay, S., … Maher, V. (2017). 15 The relationship between the buckberg index and functional capacity in stable chronic heart failure patients. *Heart*, *103*(Suppl 6), A9 LP-A10. https://doi.org/10.1136/heartjnl-2017-ICS17.15

Mansour, E. G., Gray, R., Shatila, A. H., Osborne, C. K., Tormey, D. C., Gilchrist, K. W., … Falkson, G. (1989). Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An intergroup study. *N Engl J Med*, *320*(8), 485–490. https://doi.org/10.1056/NEJM198902233200803

Mansour, E. G., Gray, R., Shatila, A. H., Tormey, D. C., Cooper, M. R., Osborne, C. K., & Falkson, G. (1998). Survival advantage of adjuvant chemotherapy in high-risk node-negative breast cancer: ten-year analysis--an intergroup study. *J Clin Oncol*, *16*(11), 3486–3492. https://doi.org/10.1200/JCO.1998.16.11.3486

Marks, L. B., Yu, X., Prosnitz, R. G., Zhou, S. M., Hardenbergh, P. H., Blazing, M., … Borges-Neto, S. (2005). The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys*, *63*(1), 214–223. https://doi.org/10.1016/j.ijrobp.2005.01.029

McEniery, C. M., Cockcroft, J. R., Roman, M. J., Franklin, S. S., & Wilkinson, I. B. (2014). Central blood pressure: current evidence and clinical importance. *European Heart Journal*,

35(26), 1719–1725. https://doi.org/10.1093/eurheartj/eht565

McEniery, C. M., Yasmin, Hall, I. R., Qasem, A., Wilkinson, I. B., & Cockcroft, J. R. (2005). Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *Journal of the American College of Cardiology*, *46*(9), 1753–1760. https://doi.org/10.1016/j.jacc.2005.07.037

McGowan, J. V, Chung, R., Maulik, A., Piotrowska, I., Walker, J. M., & Yellon, D. M. (2017). Anthracycline Chemotherapy and Cardiotoxicity. *Cardiovasc Drugs Ther*, *31*(1), 63–75. https://doi.org/10.1007/s10557-016-6711-0

McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courneya, K. S. (2006). Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ*, *175*(1), 34–41. https://doi.org/10.1503/cmaj.051073

Mehta, L. S., Watson, K. E., Barac, A., Beckie, T. M., Bittner, V., Cruz-Flores, S., … Volgman, A. S. (2018). Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. *Circulation*, *137*(8), e30–e66. https://doi.org/10.1161/CIR.0000000000000556

Mendelsohn, M. E. (2002). Protective effects of estrogen on the cardiovascular system. *The American Journal of Cardiology*, *89*(12A), 12E-17E; discussion 17E-18E.

Menna, P., Salvatorelli, E., & Minotti, G. (2008). Cardiotoxicity of antitumor drugs. *Chemical Research in Toxicology*, *21*(5), 978–989. https://doi.org/10.1021/tx800002r

Mihl, C., Dassen, W. R. M., & Kuipers, H. (2008). Cardiac remodelling: concentric versus eccentric hypertrophy in strength and endurance athletes. *Netherlands Heart Journal : Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation*, *16*(4), 129–133. https://doi.org/10.1007/bf03086131

Milan, A., Zocaro, G., Leone, D., Tosello, F., Buraioli, I., Schiavone, D., & Veglio, F. (2019). Current assessment of pulse wave velocity: comprehensive review of validation studies. *Journal of Hypertension*, *37*(8), 1547–1557. https://doi.org/10.1097/HJH.0000000000002081

Miller, K. D., Siegel, R. L., Lin, C. C., Mariotto, A. B., Kramer, J. L., Rowland, J. H., … Jemal, A. (2016). Cancer treatment and survivorship statistics, 2016. *CA: A Cancer Journal for Clinicians*, *66*(4), 271–289. https://doi.org/10.3322/caac.21349

Minotti, G, Cairo, G., & Monti, E. (1999). Role of iron in anthracycline cardiotoxicity: new tunes for an old song? *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology*, *13*(2), 199–212.

Minotti, Giorgio, Menna, P., Salvatorelli, E., Cairo, G., & Gianni, L. (2004). Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacological Reviews*, *56*(2), 185–229. https://doi.org/10.1124/pr.56.2.6

Mitchell, G. F., Wang, N., Palmisano, J. N., Larson, M. G., Hamburg, N. M., Vita, J. A., … Vasan, R. S. (2010). Hemodynamic correlates of blood pressure across the adult age

spectrum: noninvasive evaluation in the Framingham Heart Study. *Circulation*, *122*(14), 1379–1386. https://doi.org/10.1161/CIRCULATIONAHA.109.914507

Mora, S., Cook, N., Buring, J. E., Ridker, P. M., & Lee, I. M. (2007). Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation*, *116*(19), 2110–2118. https://doi.org/10.1161/CIRCULATIONAHA.107.729939

Mordente, A., Meucci, E., Silvestrini, A., Martorana, G. E., & Giardina, B. (2012). Anthracyclines and mitochondria. *Adv Exp Med Biol*, *942*, 385–419. https://doi.org/10.1007/978-94-007-2869-1_18

Mozos, I., Borzak, G., Caraba, A., & Mihaescu, R. (2017). Arterial stiffness in hematologic malignancies. *Onco Targets Ther*, *10*, 1381–1388. https://doi.org/10.2147/OTT.S126852

Mulrooney, D. A., Blaes, A. H., & Duprez, D. (2012). Vascular injury in cancer survivors. *J Cardiovasc Transl Res*, *5*(3), 287–295. https://doi.org/10.1007/s12265-012-9358-7

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*, *346*(11), 793–801. https://doi.org/10.1056/NEJMoa011858

Nakagomi, A., Shoji, T., Okada, S., Ohno, Y., & Kobayashi, Y. (2018). Validity of the augmentation index and pulse pressure amplification as determined by the SphygmoCor XCEL device: a comparison with invasive measurements. *Hypertension Research : Official Journal of the Japanese Society of Hypertension*, *41*(1), 27–32. https://doi.org/10.1038/hr.2017.81

Nakatani, S. (2011). Left ventricular rotation and twist: why should we learn? *Journal of Cardiovascular Ultrasound*, *19*(1), 1–6. https://doi.org/10.4250/jcu.2011.19.1.1

Nathan, L., Shi, W., Dinh, H., Mukherjee, T. K., Wang, X., Lusis, A. J., & Chaudhuri, G. (2001). Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(6), 3589–3593. https://doi.org/10.1073/pnas.051003698

Neil-Sztramko, S. E., Winters-Stone, K. M., Bland, K. A., & Campbell, K. L. (2019). Updated systematic review of exercise studies in breast cancer survivors: attention to the principles of exercise training. *British Journal of Sports Medicine*, *53*(8), 504–512. https://doi.org/10.1136/bjsports-2017-098389

Nichols, W. W., & McDonald, D. A. (1972). Wave-velocity in the proximal aorta. *Med Biol Eng*, *10*(3), 327–335. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/5043481

Nyrop, K.A., Deal, A. M., Shachar, S. S., Basch, E., Reeve, B. B., Choi, S. K., … Muss, H. B. (2018). Patient-Reported Toxicities During Chemotherapy Regimens in Current Clinical Practice for Early Breast Cancer. *Oncologist*. https://doi.org/10.1634/theoncologist.2018-0590

Nyrop, Kirsten A, Deal, A. M., Shachar, S. S., Basch, E., Reeve, B. B., Choi, S. K., … Muss, H. B. (2018). Patient-Reported Toxicities During Chemotherapy Regimens in Current Clinical

Practice for Early Breast Cancer. *The Oncologist*. https://doi.org/10.1634/theoncologist.2018-0590

O'Rourke, M. F., Staessen, J. A., Vlachopoulos, C., Duprez, D., & Plante, G. E. (2002). Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens*, *15*(5), 426–444. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12022246

Oliveira, N. L., Ribeiro, F., Alves, A. J., Campos, L., & Oliveira, J. (2014). The effects of exercise training on arterial stiffness in coronary artery disease patients: a state-of-the-art review. *Clinical Physiology and Functional Imaging*, *34*(4), 254–262. https://doi.org/10.1111/cpf.12093

Ottenbacher, A., Yu, M., Moser, R. P., Phillips, S. M., Alfano, C., & Perna, F. M. (2015). Population Estimates of Meeting Strength Training and Aerobic Guidelines, by Gender and Cancer Survivorship Status: Findings From the Health Information National Trends Survey (HINTS). *Journal of Physical Activity & Health*, *12*(5), 675–679. https://doi.org/10.1123/jpah.2014-0003

Overgaard, M., Jensen, M. B., Overgaard, J., Hansen, P. S., Rose, C., Andersson, M., … Mouridsen, H. T. (1999). Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet*, *353*(9165), 1641–1648. https://doi.org/10.1016/S0140-6736(98)09201-0

Overgaard, M., Jensen, M. B., Overgaard, J., Hansen, P. S., Rose, C., Andersson, M., … Zedeler, K. (1997). Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *Lancet*, *337*(14), 949–955. https://doi.org/10.1056/NEJM199710023371401

Ozemek, C., Laddu, D. R., Lavie, C. J., Claeys, H., Kaminsky, L. A., Ross, R., … Blair, S. N. (2018). An Update on the Role of Cardiorespiratory Fitness, Structured Exercise and Lifestyle Physical Activity in Preventing Cardiovascular Disease and Health Risk. *Progress in Cardiovascular Diseases*, *61*(5–6), 484–490. https://doi.org/10.1016/j.pcad.2018.11.005

Pandey, A., Parashar, A., Kumbhani, D., Agarwal, S., Garg, J., Kitzman, D., … Berry, J. (2015). Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*, *8*(1), 33–40. https://doi.org/10.1161/circheartfailure.114.001615

Paterson, D. H., Cunningham, D. A., Koval, J. J., & St Croix, C. M. (1999). Aerobic fitness in a population of independently living men and women aged 55-86 years. *Med Sci Sports Exerc*, *31*(12), 1813–1820. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10613433

Patnaik, J. L., Byers, T., DiGuiseppi, C., Dabelea, D., & Denberg, T. D. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res*, *13*(3), R64. https://doi.org/10.1186/bcr2901

Patt, D. A., Goodwin, J. S., Kuo, Y. F., Freeman, J. L., Zhang, D. D., Buchholz, T. A., … Giordano, S. H. (2005). Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol*, *23*(30), 7475–7482. https://doi.org/10.1200/JCO.2005.13.755

Peel, A. B., Thomas, S. M., Dittus, K., Jones, L. W., & Lakoski, S. G. (2014). Cardiorespiratory fitness in breast cancer patients: a call for normative values. *J Am Heart Assoc*, *3*(1), e000432. https://doi.org/10.1161/JAHA.113.000432

Peel, J. B., Sui, X., Adams, S. A., Hebert, J. R., Hardin, J. W., & Blair, S. N. (2009). A prospective study of cardiorespiratory fitness and breast cancer mortality. *Med Sci Sports Exerc*, *41*(4), 742–748. https://doi.org/10.1249/MSS.0b013e31818edac7

Peng, X., Chen, B., Lim, C. C., & Sawyer, D. B. (2005). The cardiotoxicology of anthracycline chemotherapeutics: translating molecular mechanism into preventative medicine. *Molecular Interventions*, *5*(3), 163–171. https://doi.org/10.1124/mi.5.3.6

Peto, R., Davies, C., Godwin, J., Gray, R., Pan, H. C., Clarke, M., … Pritchard, K. (2012). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet (London, England)*, *379*(9814), 432–444. https://doi.org/10.1016/S0140-6736(11)61625-5

Piccart-Gebhart, M. J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., … Herceptin Adjuvant Trial Study, T. (2005). Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*, *353*(16), 1659–1672. https://doi.org/10.1056/NEJMoa052306

Poole, D. C., Copp, S. W., Ferguson, S. K., & Musch, T. I. (2013). Skeletal muscle capillary function: contemporary observations and novel hypotheses. *Experimental Physiology*, *98*(12), 1645–1658. https://doi.org/10.1113/expphysiol.2013.073874

Reference Values for Arterial Stiffness, C. (2010). Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: "establishing normal and reference values." *Eur Heart J*, *31*(19), 2338–2350. https://doi.org/10.1093/eurheartj/ehq165

Rikli, R. E., & Jones, C. J. (2013). Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. *The Gerontologist*, *53*(2), 255–267. https://doi.org/10.1093/geront/gns071

Rochais, F., & Fischmeister, R. (2010). Acute cardiac effects of neuregulin-1/ErbB signalling. *Cardiovasc Res*, *88*(3), 393–394. https://doi.org/10.1093/cvr/cvq316

Rock, C. L., Flatt, S. W., Newman, V., Caan, B. J., Haan, M. N., Stefanick, M. L., … Pierce, J. P. (1999). Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. *J Am Diet Assoc*, *99*(10), 1212–1221. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10524383

Romond, E. H., Perez, E. A., Bryant, J., Suman, V. J., Geyer Jr., C. E., Davidson, N. E., … Wolmark, N. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive

breast cancer. *N Engl J Med*, *353*(16), 1673–1684. https://doi.org/10.1056/NEJMoa052122

Runowicz, C. D., Leach, C. R., Henry, N. L., Henry, K. S., Mackey, H. T., Cowens-Alvarado, R. L., … Ganz, P. A. (2016). American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol*, *34*(6), 611–635. https://doi.org/10.1200/JCO.2015.64.3809

Rygiel, K. (2017). Cardiotoxic effects of radiotherapy and strategies to reduce them in patients with breast cancer: An overview. *Journal of Cancer Research and Therapeutics*, *13*(2). https://doi.org/10.4103/0973-1482.187303

Sandoo, A., Kitas, G. D., & Carmichael, A. R. (2015). Breast cancer therapy and cardiovascular risk: focus on trastuzumab. *Vasc Health Risk Manag*, *11*, 223–228. https://doi.org/10.2147/VHRM.S69641

Sanoff, H. K., Deal, A. M., Krishnamurthy, J., Torrice, C., Dillon, P., Sorrentino, J., … Muss, H. B. (2014). Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. *Journal of the National Cancer Institute*, *106*(4), dju057. https://doi.org/10.1093/jnci/dju057

Santos, W. D. N. Dos, Vieira, A., de Lira, C. A. B., Mota, J. F., Gentil, P., de Freitas Junior, R., … Vieira, C. A. (2019). Once a Week Resistance Training Improves Muscular Strength in Breast Cancer Survivors: A Randomized Controlled Trial. *Integrative Cancer Therapies*, *18*, 1534735419879748–1534735419879748. https://doi.org/10.1177/1534735419879748

Sasso, J. P., Eves, N. D., Christensen, J. F., Koelwyn, G. J., Scott, J., & Jones, L. W. (2015, June). A framework for prescription in exercise-oncology research. *Journal of Cachexia, Sarcopenia and Muscle*. Germany. https://doi.org/10.1002/jcsm.12042

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., … American College of Sports, M. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*, *42*(7), 1409–1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

Schmitz, K. H., DiSipio, T., Gordon, L. G., & Hayes, S. C. (2015). Adverse breast cancer treatment effects: the economic case for making rehabilitative programs standard of care. *Support Care Cancer*, *23*(6), 1807–1817. https://doi.org/10.1007/s00520-014-2539-y

Schmitz, K. H., Prosnitz, R. G., Schwartz, A. L., & Carver, J. R. (2012). Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer*, *118*(8 Suppl), 2270–2276. https://doi.org/10.1002/cncr.27462

Scott, J M, Adams, S. C., Koelwyn, G. J., & Jones, L. W. (2016). Cardiovascular Late Effects and Exercise Treatment in Breast Cancer: Current Evidence and Future Directions. *Can J Cardiol*, *32*(7), 881–890. https://doi.org/10.1016/j.cjca.2016.03.014

Scott, J M, Jones, L. W., Hornsby, W. E., Koelwyn, G. J., Khouri, M. G., Joy, A. A., … Lakoski, S. G. (2014). Cancer therapy-induced autonomic dysfunction in early breast cancer: implications for aerobic exercise training. *Int J Cardiol*, *171*(2), e50-1.

https://doi.org/10.1016/j.ijcard.2013.11.113

Scott, J M, Zabor, E. C., Schwitzer, E., Koelwyn, G. J., Adams, S. C., Nilsen, T. S., … Jones, L. W. (2018). Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol*, JCO2017775809. https://doi.org/10.1200/JCO.2017.77.5809

Scott, Jessica M, Nilsen, T. S., Gupta, D., & Jones, L. W. (2018). Exercise Therapy and Cardiovascular Toxicity in Cancer. *Circulation*, *137*(11), 1176–1191. https://doi.org/10.1161/CIRCULATIONAHA.117.024671

Seidman, A., Hudis, C., Pierri, M. K., Shak, S., Paton, V., Ashby, M., … Keefe, D. (2002). Cardiac dysfunction in the trastuzumab clinical trials experience. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *20*(5), 1215–1221. https://doi.org/10.1200/JCO.2002.20.5.1215

Shapiro, C. L., Hardenbergh, P. H., Gelman, R., Blanks, D., Hauptman, P., Recht, A., … Henderson, I. C. (1998). Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. *J Clin Oncol*, *16*(11), 3493–3501. https://doi.org/10.1200/JCO.1998.16.11.3493

Shiels, H. A., & White, E. (2008). The Frank-Starling mechanism in vertebrate cardiac myocytes. *The Journal of Experimental Biology*, *211*(Pt 13), 2005–2013. https://doi.org/10.1242/jeb.003145

Shiovitz, S., & Korde, L. A. (2015). Genetics of breast cancer: a topic in evolution. *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *26*(7), 1291–1299. https://doi.org/10.1093/annonc/mdv022

Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics, 2015. *CA Cancer J Clin*, *65*(1), 5–29. https://doi.org/10.3322/caac.21254

Slamon, D., Eiermann, W., Robert, N., Pienkowski, T., Martin, M., Press, M., … Breast Cancer International Research, G. (2011). Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*, *365*(14), 1273–1283. https://doi.org/10.1056/NEJMoa0910383

Slamon, D. J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., … Norton, L. (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*, *344*(11), 783–792. https://doi.org/10.1056/NEJM200103153441101

Souza, C. A. de, Simoes, R., Borges, K. B. G., Oliveira, A. N. de, Zogeib, J. B., Alves, B., … Rezende, B. A. (2018). Arterial Stiffness Use for Early Monitoring of Cardiovascular Adverse Events due to Anthracycline Chemotherapy in Breast Cancer Patients. A Pilot Study. *Arquivos Brasileiros de Cardiologia*, *111*(5), 721–728. https://doi.org/10.5935/abc.20180168

Spallarossa, P., Altieri, P., Pronzato, P., Aloi, C., Ghigliotti, G., Barsotti, A., & Brunelli, C. (2010). Sublethal doses of an anti-erbB2 antibody leads to death by apoptosis in

cardiomyocytes sensitized by low prosenescent doses of epirubicin: the protective role of dexrazoxane. *J Pharmacol Exp Ther*, *332*(1), 87–96. https://doi.org/10.1124/jpet.109.159525

Sparano, J. A., Gray, R. J., Makower, D. F., Pritchard, K. I., Albain, K. S., Hayes, D. F., … Sledge, G. W. J. (2018). Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *The New England Journal of Medicine*, *379*(2), 111–121. https://doi.org/10.1056/NEJMoa1804710

Sturgeon, K. M., Deng, L., Bluethmann, S. M., Zhou, S., Trifiletti, D. M., Jiang, C., … Zaorsky, N. G. (2019). A population-based study of cardiovascular disease mortality risk in US cancer patients. *European Heart Journal*. https://doi.org/10.1093/eurheartj/ehz766

Sugawara, J., Komine, H., Hayashi, K., Yoshizawa, M., Otsuki, T., Shimojo, N., … Tanaka, H. (2007). Systemic alpha-adrenergic and nitric oxide inhibition on basal limb blood flow: effects of endurance training in middle-aged and older adults. *American Journal of Physiology. Heart and Circulatory Physiology*, *293*(3), H1466-72. https://doi.org/10.1152/ajpheart.00273.2007

Sutton-Tyrrell, K., Najjar, S. S., Boudreau, R. M., Venkitachalam, L., Kupelian, V., Simonsick, E. M., … Health, A. B. C. S. (2005). Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*, *111*(25), 3384–3390. https://doi.org/10.1161/CIRCULATIONAHA.104.483628

Swain, S. M., Whaley, F. S., & Ewer, M. S. (2003). Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*, *97*(11), 2869–2879. https://doi.org/10.1002/cncr.11407

Swartz, M. C., Lewis, Z. H., Lyons, E. J., Jennings, K., Middleton, A., Deer, R. R., … Goodwin, J. S. (2017). Effect of Home- and Community-Based Physical Activity Interventions on Physical Function Among Cancer Survivors: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, *98*(8), 1652–1665. https://doi.org/https://doi.org/10.1016/j.apmr.2017.03.017

Sweegers, M. G., Altenburg, T. M., Brug, J., May, A. M., van Vulpen, J. K., Aaronson, N. K., … Buffart, L. M. (2019). Effects and moderators of exercise on muscle strength, muscle function and aerobic fitness in patients with cancer: a meta-analysis of individual patient data. *British Journal of Sports Medicine*, *53*(13), 812 LP – 812. https://doi.org/10.1136/bjsports-2018-099191

Sweegers, M. G., Altenburg, T. M., Chinapaw, M. J., Kalter, J., Verdonck-de Leeuw, I. M., Courneya, K. S., … Buffart, L. M. (2018). Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. *British Journal of Sports Medicine*, *52*(8), 505 LP – 513. https://doi.org/10.1136/bjsports-2017-097891

Tan-Chiu, E., Yothers, G., Romond, E., Geyer Jr., C. E., Ewer, M., Keefe, D., … Bryant, J. (2005). Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and

cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast can. *J Clin Oncol*, *23*(31), 7811–7819. https://doi.org/10.1200/JCO.2005.02.4091

Thurlimann, B., Keshaviah, A., Coates, A. S., Mouridsen, H., Mauriac, L., Forbes, J. F., … Goldhirsch, A. (2005). A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *The New England Journal of Medicine*, *353*(26), 2747–2757. https://doi.org/10.1056/NEJMoa052258

Tsygankov, D., Liu, Y., Sanoff, H. K., Sharpless, N. E., & Elston, T. C. (2009). A quantitative model for age-dependent expression of the p16INK4a tumor suppressor. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(39), 16562–16567. https://doi.org/10.1073/pnas.0904405106

Vaitkevicius, P. V, Fleg, J. L., Engel, J. H., O'Connor, F. C., Wright, J. G., Lakatta, L. E., … Lakatta, E. G. (1993). Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*, *88*(4 Pt 1), 1456–1462.

Vallerio, P., Sarno, L., Stucchi, M., Musca, F., Casadei, F., Maloberti, A., … Giannattasio, C. (2016). Long-Term Effects of Radiotherapy on Arterial Stiffness in Breast Cancer Women. *Am J Cardiol*, *118*(5), 771–776. https://doi.org/10.1016/j.amjcard.2016.06.001

van Waart, H., Stuiver, M. M., van Harten, W. H., Geleijn, E., Kieffer, J. M., Buffart, L. M., … Aaronson, N. K. (2015). Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *33*(17), 1918–1927. https://doi.org/10.1200/JCO.2014.59.1081

Veronesi, U., Luini, A., Del Vecchio, M., Greco, M., Galimberti, V., Merson, M., … et al. (1993). Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med*, *328*(22), 1587–1591. https://doi.org/10.1056/NEJM199306033282202

Vlachopoulos, C., Aznaouridis, K., O'Rourke, M. F., Safar, M. E., Baou, K., & Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *European Heart Journal*, *31*(15), 1865–1871. https://doi.org/10.1093/eurheartj/ehq024

Vlachopoulos, C., Aznaouridis, K., & Stefanadis, C. (2010a). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *Journal of the American College of Cardiology*, *55*(13), 1318–1327. https://doi.org/10.1016/j.jacc.2009.10.061

Vlachopoulos, C., Aznaouridis, K., & Stefanadis, C. (2010b). Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness. A Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology*, *55*(13), 1318–1327. https://doi.org/10.1016/j.jacc.2009.10.061

Von Hoff, D. D., Layard, M. W., Basa, P., Davis Jr., H. L., Von Hoff, A. L., Rozencweig, M., & Muggia, F. M. (1979). Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*, *91*(5), 710–717. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/496103

Wagoner, C. W., Choi, S. K., Deal, A. M., Lee, J. T., Wood, W. A., Muss, H. B., & Nyrop, K. A. (2019). Establishing physical activity in breast cancer: self-report versus activity tracker. *Breast Cancer Research and Treatment*. https://doi.org/10.1007/s10549-019-05263-3

Wagoner, C. W., Hanson, E. D., Ryan, E. D., Brooks, R., Wood, W. A., Jensen, B. C., … Battaglini, C. L. (2019). Two weeks of lower body resistance training enhances cycling tolerability to improve precision of maximal cardiopulmonary exercise testing in sedentary middle-aged females. *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition et Metabolisme*, *44*(11), 1159–1164. https://doi.org/10.1139/apnm-2018-0623

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006a). Health benefits of physical activity: the evidence. *CMAJ : Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *174*(6), 801–809. https://doi.org/10.1503/cmaj.051351

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006b). Prescribing exercise as preventive therapy. *CMAJ : Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *174*(7), 961–974. https://doi.org/10.1503/cmaj.1040750

Wassertheurer, S., Kropf, J., Weber, T., van der Giet, M., Baulmann, J., Ammer, M., … Magometschnigg, D. (2010). A new oscillometric method for pulse wave analysis: comparison with a common tonometric method. *Journal of Human Hypertension*, *24*(8), 498–504. https://doi.org/10.1038/jhh.2010.27

Weber, T., Auer, J., O'Rourke, M. F., Kvas, E., Lassnig, E., Berent, R., & Eber, B. (2004). Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*, *109*(2), 184–189. https://doi.org/10.1161/01.CIR.0000105767.94169.E3

Weiss, R. B. (1992). The anthracyclines: will we ever find a better doxorubicin? *Semin Oncol*, *19*(6), 670–686. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1462166

Wilkerson, D. P., Poole, D. C., Jones, A. M., Fulford, J., Mawson, D. M., Ball, C. I., & Shore, A. C. (2011). Older type 2 diabetic males do not exhibit abnormal pulmonary oxygen uptake and muscle oxygen utilization dynamics during submaximal cycling exercise. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *300*(3), R685-92. https://doi.org/10.1152/ajpregu.00479.2010

Williams, B., Lacy, P. S., Thom, S. M., Cruickshank, K., Stanton, A., Collier, D., … Writing, C. (2006). Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*, *113*(9), 1213–1225. https://doi.org/10.1161/CIRCULATIONAHA.105.595496

Willum-Hansen, T., Staessen, J. A., Torp-Pedersen, C., Rasmussen, S., Thijs, L., Ibsen, H., &

Jeppesen, J. (2006). Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*, *113*(5), 664–670. https://doi.org/10.1161/CIRCULATIONAHA.105.579342

Wilson, M. G., Ellison, G. M., & Cable, N. T. (2016). Basic science behind the cardiovascular benefits of exercise. *British Journal of Sports Medicine*, *50*(2), 93–99. https://doi.org/10.1136/bjsports-2014-306596rep

Wilson, P. W. F., D'Agostino, R. B., Sullivan, L., Parise, H., & Kannel, W. B. (2002). Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Archives of Internal Medicine*, *162*(16), 1867–1872.

Yersal, O., Eryilmaz, U., Akdam, H., Meydan, N., & Barutca, S. (2018). Arterial Stiffness in Breast Cancer Patients Treated with Anthracycline and Trastuzumab-Based Regimens. *Cardiology Research and Practice*, *2018*, 5352914. https://doi.org/10.1155/2018/5352914

Yu, A. F., & Jones, L. W. (2016). Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. *Cardiooncology*, *2*. https://doi.org/10.1186/s40959-016-0011-5

Yu, Z., Guo, X., Jiang, Y., Teng, L., Luo, J., Wang, P., … Zhang, H. (2017). Adjuvant endocrine monotherapy for postmenopausal early breast cancer patients with hormone-receptor positive: a systemic review and network meta-analysis. *Breast Cancer*. https://doi.org/10.1007/s12282-017-0794-8

Yusuf, S. W., Sami, S., & Daher, I. N. (2011). Radiation-induced heart disease: a clinical update. *Cardiol Res Pract*, *2011*, 317659. https://doi.org/10.4061/2011/317659

Zagar, T. M., Cardinale, D. M., & Marks, L. B. (2016). Breast cancer therapy-associated cardiovascular disease. *Nature Reviews Clinical Oncology*. https://doi.org/10.1038/nrclinonc.2015.171

Zaydun, G., Tomiyama, H., Hashimoto, H., Arai, T., Koji, Y., Yambe, M., … Yamashina, A. (2006). Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early postmenopausal phase. *Atherosclerosis*, *184*(1), 137–142. https://doi.org/10.1016/j.atherosclerosis.2005.03.043

Zeglinski, M., Ludke, A., Jassal, D. S., & Singal, P. K. (2011). Trastuzumab-induced cardiac dysfunction: A "dual-hit." *Exp Clin Cardiol*, *16*(3), 70–74. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22065936